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Research Article

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Rapid assessment of sedimentation stability in Paracetamol suspension formulations with different suspending agents using near infrared transmission measurements

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ABSTRACT

The aim of the study is to formulate paracetamol suspensions and evaluate their sedimentation stability in a rapid way by employing near infrared transmission measurements. The mucilage extracted from Plantago ovata seeds was also used as one of the suspending agents. The mucilage is a natural suspending agent that can be used as an effective alternative for traditional suspending agents. Stability studies of suspensions are very important to enable the patient to receive the intended amount of the drug(s) in the dose administered. Physical stability of paracetamol 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). Paracetamol 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 determined on different suspension formulations indicated that MC and POM are preferable suspending agents for the preparation of stable suspensions of paracetamol.

Key words: suspension, physical stability, separation analyzer, LUMiReader®, STEP-Technology, instability index.

INTRODUCTION

Suspensions are biphasic heterogeneous coarse dispersions containing essentially the insoluble particulate matter or drug suspended with the help of suspending agent(s) in a liquid medium. The continuous or external phase is generally a liquid or semisolid. The liquid phase may be aqueous or in some instances may be organic or oily liquid for non oral use. The dispersed or internal phase is the insoluble particulate matter dispersed throughout the continuous or external phase. These are thermodynamically unstable; almost all suspension systems separate on standing. Because some products occasionally are prepared in a dry form to be placed in suspension at the time of dispensing by the addition of an appropriate liquid vehicle, this definition is extended to include these products [1, 2].

Stability study of suspensions is a very important aspect to enable the patient to receive the intended amount of the drug(s) in the dose administered. Physico-chemical stability of suspensions is important for maintaining the quality of the product. Paracetamol is N- acetyl- P- aminophenol, 4-hydroxyacetanilide, $C_8H_9NO_2$ (151.16). It is a major metabolite of phenacetin (p- ethoxy acetanilide) and an effective antipyretic and analgesic agent with mechanism similar to that of the salicylates. It produces antipyresis by acting on the hypothalamic heat- regulating centre and analgesic by elevating the pain threshold. It is useful particularly as an analgesic- antipyretic in patients who

experience untoward reactions to aspirin. Unlike aspirin, acetaminophen does not antagonize the effects of uricosuric agents. The drug structure is shown under Figure 1.

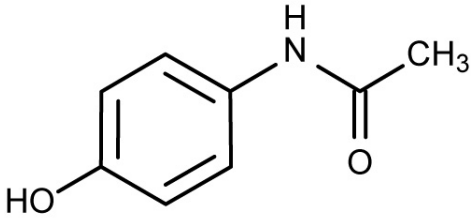


Figure1: Structure of paracetamol

Physical stability testing of paracetamol suspensions

Different procedures have been suggested in the past for evaluating the physical stability of suspensions [3-6]. Some of these are experiential 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 well be classified into:
1. Sedimentation methods
2. Rheological methods
3. Electro-kinetic methods and
4. 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.

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 [7]. By using an instrument called LUMiReader® which operates on STEP-Technology, it is possible to observe and understand different stability/instability phenomena of a suspension 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 settling, creaming and consolidation (separation velocity)
- The Integral Transmission for the clarification speed
- The PSA-Module for the calculation of the particle size distribution.
- Stability analysis for determination of instability index and for comparison of stability of different samples.

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 paracetamol suspensions formulated with different suspending agents. The sample cell in a LUMiReader® is illuminated by a multi-colour light source I_0, 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 (I_0/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 [8,9] at different wavelengths for sedimenting or creaming particles in gravitational or centrifugal field.

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. Particle size distribution is obtained based on Stokes' law [7]. Mostly 2 mm cells made of polycarbonate are used for measurements (sample volume 0.4 cm^3). For samples with very low turbidity 10 mm cells (sample volume 2 cm^3) are used alternatively.

EXPERIMENTAL SECTION

Materials: Paracetamol IP was procured from SS Pharmachem, Cuttack, 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. [10]. 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.

Compatibility studies

Compatibility studies were carried out to investigate the incompatibilities between paracetamol 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 paracetamol and suspending agents were prepared by trituration in a clean and dry glass mortar and pestle [11]. 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.

Preparation of paracetamol suspensions

Paracetamol 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 paracetamol suspensions

Formulation code	Amount of paracetamol (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

MC- Methylcellulose; HPMC K4M – Hydroxypropyl methylcellulose K4M; SCMC- Sodium carboxymethylcellulose; POM- Plantango ovata mucilage

Procedure

The suspending agent was kept in contact with about 90 ml of water containing 100 mg of sodium benzoate for 12 hours to allow swelling of the suspending agent. The dispersion was thoroughly mixed with a laboratory stirrer (REMI) for 30 minutes at an average speed of 200 rpm to get a uniform dispersion. Paracetamol was then added to the dispersion under stirring and stirring continued for another 30 minutes and made up to volume. The prepared suspensions were stored at room temperature until further studies.

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 basing on the sample properties like freedom from organic solvents, viscosity of the suspensions etc., as recommended by the manufacturer of the instrument.

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, vial 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 [7]. 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.

Some of the representative profiles recorded are shown in Figure 2 and Figure 3. The relevant data is shown in Table 2 and Table 3.

Figure 2: Extinction profiles for paracetamol suspension containing 0.5% of HPMCK4M as suspending agent measured at 30º tilt and 30 ºC temperature: Stability analysis – instability index

LUM

Stability Analysis

Analysis Summary

Title of Analysis:	P HPMC 0.5% Sample 2 (c) 1 h 0 s 130p 30°-30° 1-1 60 20150224 16:03:26
Saved:	Analysis not saved
User:	admin
Samples:	[870 nm] P HPMC 0.5% C [630 nm] P HPMC 0.5% C [470 nm] P HPMC 0.5% C
Normalization:	Normalization applied, dynamic baseline correction
Smoothing:	Moving Average (9 points)
Notes:	

Data Range Analysed:

Sample Name	Range from in mm	Range to in mm	Range in mm	Time in s	Channel/ Wavelength
[870 nm] P HPMC 0.5% C	5.04	19.04	14.00	3,595.59	870 nm
[630 nm] P HPMC 0.5% C	17.76	31.76	14.00	3,595.59	630 nm
[470 nm] P HPMC 0.5% C	13.18	27.18	14.00	3,595.59	470 nm

Results:

Sample Name	Time in s	Instability Index	Mean RCA in g	Mean	StdDev
[870 nm] P HPMC 0.5% C	3,596	0.8320	-∞	0.7758	0.1871
[630 nm] P HPMC 0.5% C	3,536	0.4658	-∞	0.4319	0.1180
[470 nm] P HPMC 0.5% C	3,536	0.7895	-∞	0.7283	0.1936

Details for Sample: [870 nm] P HPMC 0.5% C

Measurement Title:	P HPMC 0.5% Sample 2 (c) 1 h 0 s 130p 30°-30° 1-1 60 20150224 16:03:26
Sample Name:	[870 nm] P HPMC 0.5% C
Channel:	1
Wavelength:	870 nm
Sample GUID:	{967CCD27-D07F-4299-8A8A-A4490119203F}
Measurement Date:	Tuesday, February 24, 2015 4:03:26 PM
Device:	LUMiReader 4532-109 (1 channel)
Sample Cell:	[6] LUM 10mm, PC, Rect. Synthetic Cell (110-132xx)
Meniscus:	5.04 mm
Notes:	

SOP

#	Profiles	Interval	Tilt	Light Factor
1	50	10s	30°	1.00
2	50	30s	30°	1.00
3	20	50s	30°	1.00
4	10	60s	30°	1.00

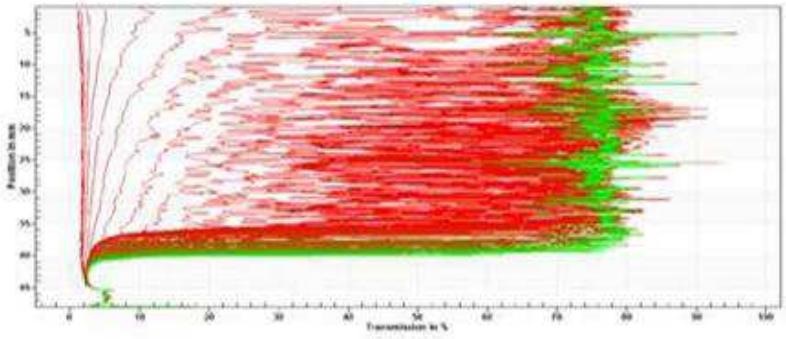


Figure 3. Extinction profiles for paracetamol suspension containing 0.5% of HPMCK4M as suspending agent measured at 30º tilt and 30 ºC temperature: Front tracking – sedimentation velocity

LUM

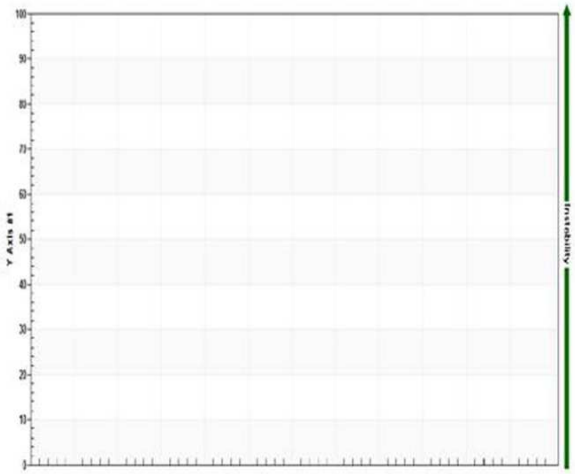
Front Tracking

Analysis Summary

Title of Analysis:	P HPMC 0.5% Sample 2 (c) 1 h 0 s 130p 30°-30° 1-1 60 20150224 16:03:26
Saved:	Analysis not saved
Separation Process:	Sedimentation
User:	admin
Samples:	[870 nm] P HPMC 0.5% C [630 nm] P HPMC 0.5% C [470 nm] P HPMC 0.5% C
Normalization:	Normalization applied, dynamic baseline correction
Smoothing:	Moving Average (9 points)
Notes:	

Data Range Analysed:

Sample Name	Range from in mm	Range to in mm	Threshold in %	Start in s	End in s	Channel/ Wavelength
[870 nm] P HPMC 0.5% C	5.04	19.04	12.00	0.00	3,595.59	870 nm
[630 nm] P HPMC 0.5% C	17.76	31.76	12.00	0.00	3,595.59	630 nm
[470 nm] P HPMC 0.5% C	13.18	27.18	12.00	0.00	3,595.59	470 nm



Results:

Sample Name	Start in s	End in s	Value at End in µm	Mean RCA in g	Velocity in µm/s	StdDev in µm/s
[870 nm] P HPMC 0.5% C	63.86	73.86	18,139	-x-	832.6	-x-
[630 nm] P HPMC 0.5% C	83.60	3,593	31,516	-x-	5,623	0.0169
[470 nm] P HPMC 0.5% C	73.68	83.78	23,513	-x-	1,023	-x-

Sample Name	Intercept in µm	StdDev in µm	Corr. coeff.	Mean in µm	StdDev in µm
[870 nm] P HPMC 0.5% C	-43,355	-x-	1.000	13,976	5,887
[630 nm] P HPMC 0.5% C	18,506	-x-	0.5934	29,581	3,661
[470 nm] P HPMC 0.5% C	-62,174	-x-	1.000	18,348	7,304

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 1 month. The test was performed on samples in triplicate by shaking the sedimented suspensions manually at 180° movement, after sedimentation was completed [12]. Based on the numbers of shaking 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.

RESULTS AND DISCUSSION

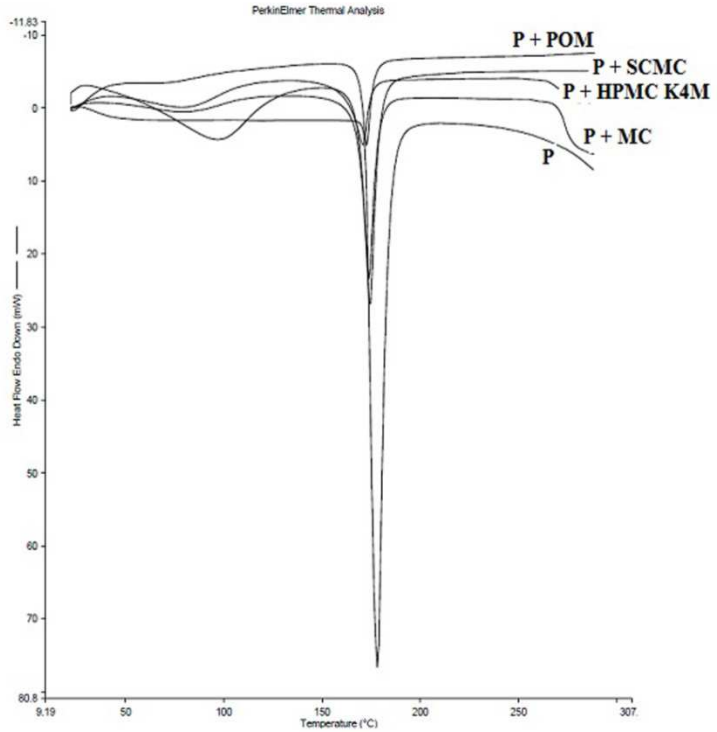
Compatibility studies

DSC Studies

Result of DSC study shown in Figure 4 describes thermal behaviour of paracetamol with MC, HPMC, SCMC and POM.

DSC thermograms of paracetamol and the 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 paracetamol had undergone thermal transition at 178.16 °C (melting endotherm of paracetamol), 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 paracetamol and pure suspending agents were retained in the physical mixture during the study period at the storage condition. In the physical mixtures of paracetamol with each of the suspending agents, the thermal transitions occurring at 178.16 °C were not affected as shown in Figure 4, 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.

Figure 4: DSC thermograms of paracetamol (P) and mixtures of paracetamol and suspending agents



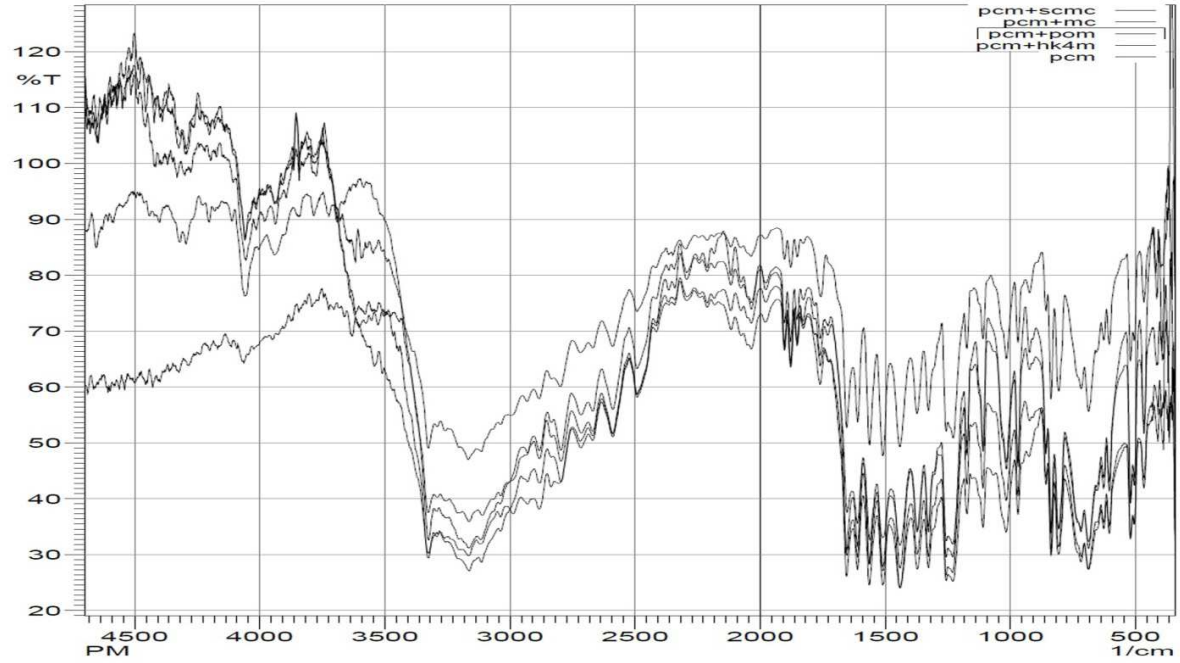
P- Paracetamol; MC- methylcellulose; HPMC K4M – Hydroxypropyl methyl cellulose K4M; SCMC- Sodium carboxymethylcellulose; POM- Plantango ovata mucilage

FT-IR Studies

Compatibility of paracetamol 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 paracetamol showed various prominent and characteristic peaks. The characteristic broad and strong peak around 3500cm^{-1} indicates the presence of O-H stretching, the presence of peak at 1651cm^{-1} indicates C=O stretching for amide group. The spike at 3563 cm^{-1} indicates the presence of N-H stretching. The peak at 2900 cm^{-1} indicates the presence of C-H stretching. The peak around 3100 cm^{-1} indicates the presence of aromatic C-H stretching. The presence of characteristic spikes for O-H stretching, C=O stretching, N-H stretching, C-H stretching and no new bands or shift in characteristic peaks appeared in the physical mixtures of paracetamol with different suspending agents as shown in Figure 5 indicated that there was no significant interaction between the drug and the selected suspending agents.

Figure 5: FTIR spectra of paracetamol and mixtures of PCM and suspending agents



Preparation of paracetamol 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, HPMC K4 M, 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.

Determination of physical stability of suspensions

Determination of instability index and sedimentation velocity of suspensions

Separation analyser LUMiReader® PSA 453 was employed for stability determinations. 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.

Table 2. LUMiReader® stability data for paracetamol 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	0.051	0.046	0.0748	0.115	4.237	7.452	7.868	8.457
HPMC K4M	0.634	0.675	0.6645	0.672	5.363	7.563	15.256	16.63
SCMC	0.431	0.543	0.566	0.572	94.23	105.4	112.4	154.5
POM	0.101	0.122	0.125	0.142	0.001	-x-	-x-	-x-

Table 3. LUMiReader® stability data for paracetamol suspensions at 30º 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	0.062	0.052	0.083	0.185	5.557	8.322	8.588	9.873
HPMC K4M	0.842	0.832	0.754	0.722	6.465	832.6	183.2	205.4
SCMC	0.632	0.746	0.584	0.554	132.3	145.2	152.6	180.5
POM	0.153	0.153	0.154	0.158	0.154	-x-	-x-	-x-

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

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 profiles were automatically saved 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 (0.052) with suspension formulation containing 0.5 % of MC. The instability index was 0.153 with suspensions with 0.25 % to 0.5 % POM as suspending agent. It was the highest (0.842) with formulation containing 0.5 % 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 MC or 0.25 to 0.5 % of POM are suitable suspending agents for preparation of stable suspensions of paracetamol.

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 of resuspendability are given under Table 4.

Results shown in Table 4 indicate that the formulations containing MC and POM were easily resuspendable compared to suspensions containing HPMC and SCMC as suspending agents as they required less number of shakings for obtaining uniform dispersion.

Table 4: Results of resuspendability evaluation on paracetamol suspensions (n=3)

Sample	Suspending agent	% of suspending agent	Number of shakings required to get a uniform dispersion (average of 3 findings)	Caking
F1S1	MC	0.25	1.00	No
F2S1	MC	0.50	1.33	No
F3S1	MC	0.75	2.33	No
F4S1	MC	1.00	5.66	No
F1S2	HPMCK4M	0.25	5.33	No
F2S2	HPMCK4M	0.50	7.66	No
F3S2	HPMCK4M	0.75	5.33	No
F4S2	HPMCK4M	1.00	6.33	No
F1S3	SCMC	0.25	3.00	No
F2S3	SCMC	0.50	4.33	No
F3S3	SCMC	0.75	2.33	No
F4S3	SCMC	1.00	4.33	No
F1S4	POM	0.25	1.33	No
F2S4	POM	0.50	2.66	No
F3S4	POM	0.75	2.33	No
F4S4	POM	1.00	3.33	No

Considering the results of instability index, sedimentation velocity and resuspendability of the suspensions it can be further inferred that 0.5 % of MC or 0.25 to 0.50 % of POM can be considered suitable as suspending agents for preparation of stable suspensions of paracetamol. Further the FT-IR and DSC studies showed that the selected suspending agents were compatible with paracetamol. The experimental data indicate the following decreasing order of preference of suspending agents for paracetamol suspensions: MC > POM (0.25 to 0.5%) > SCMC > HPMCK4M in a concentration range of 0.5 to 1.0 %.

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 paracetamol suspensions.

Order of preference of suspending agents: MC > POM (0.25 to 0.5%) > SCMC > HPMCK4M in a concentration range of 0.5 to 1.0 %.

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