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### Studies on Physical Stability of Rofecoxib Oral Suspension Using Controlled Flocculation Approach

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#### ABSTRACT

Rofecoxib a selective Cox-2 inhibitor indicated to the treatment of osteoarthritis and management of acute pain and treatment of primary dysmenorrhea and is superior to other NSAID due to lower incidence of bleeding and other gastro-toxic effects. The present work was aimed to formulating physically stable Rofecoxib suspension using controlled flocculation approach. The ability to different flocculating agents to flocculate Rofecoxib suspensions studied it is also proposed to access the physical stability of the prepared formulations by performing stability studies according to ICH guidelines. U.V Spectro Photometric Method was selected for assay as well as in-vitro dissolution studies at 237 nm. From the stability studies it was found that the suspension containing veegum +calcium chloride was the best formulation among all the suspensions prepared.

**Keywords:** Rofecoxib, Suspensions, Physical Stability, Controlled Flocculation.

#### INTRODUCTION

Suspensions are liquid preparations that consist of solid particles dispersed throughout a liquid phase in which the particles are not soluble or an insoluble drug or other substance in an aqueous or non-aqueous continuous phase (USP, 2000). In colloidal suspension, the particle size of the solids is less than about 1 $\mu$ m in size. When the particles are greater than about 1  $\mu$ m the system is called a 'coarse suspension'. The practical upper limit for individual suspendable solid particles in coarse suspensions is approximately 50-75 $\mu$ m (Hiestand E N,1964). Stability studies of suspension are an area of ongoing research. Many of the more recently developed drugs are poorly water soluble in nature. Thus solutions of these drugs, containing an appropriate dosage, would be of an unacceptably large volume. Suspensions allow the development of a liquid dosage form containing an appropriate quantity of drug in reasonably small volume. Further, resistance to hydrolysis and oxidation is generally good compared with the observations in aqueous solution. Suspension can also be used to mask the taste of drugs. Also there is a significant proportion

of the population, especially very young children, who have difficulty in swallowing tablets or capsules. In recent years, increasing attention has been given to the use of suspension in intramuscular injection for depot therapy. The suspension offers greater chemical stability since the drug is not in solution and in some cases enhanced bioavailability results (Gibaldi M, 1971). Decreasing the particle size of the drug may also enhance bioavailability. Also delayed drug absorption resulting in prolonged duration of action, attributed to an increase in the viscosity of the vehicle in parenteral suspensions is possible (Soci MM *et al.*, 1980). Formulation of an effective and pharmaceutically elegant suspension is usually much harder to achieve than that of a tablet or capsule of the same drug (Christopher T *et al.*, 1990). Suspension is one of the most acceptable dosage forms for paediatric patients hence always a thrust area of research for formulation scientist.

Suspensions as dosage forms are becoming increasingly popular in recent years for Paediatric purposes. Today, many drugs are available in commercial market in the form of suspensions, for example, Paracetamol, Ibuprofen, Metronidazole benzoate, Nimesulide, etc. An efficient formulation of suspension requires various additives like suspending agents, wetting agents, preservatives and other excipients, all of which have their own effects on physical stability of the dosage

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form. Evaluation of physical stability of suspension is an area of ongoing research. The efficiency of a suspension is related to the efficient dispersion of drug particles in the vehicle at the time of dosing. Patient compliance is difficult to assure, if redispersibility is poor. Physical stability of suspension may be defined as the condition in which the particles do not aggregate and in which they remain uniformly distributed throughout the dispersion. Since this ideal situation is seldom realized it is appropriate to add the statement that if the particles do settle, they should be easily resuspended by a moderate amount of agitation. After preparing the deflocculated dispersion, the controlled flocculation is then attempted by the use of flocculating agent. The aim is to add that concentration, which result in the maximum sedimentation volume, for under these conditions caking is minimized

The present work was aimed at formulating physically stable Rofecoxib suspensions using controlled flocculation approach. The ability of different flocculating agents to flocculate Rofecoxib suspensions was studied. It was also proposed to assess the physical stability of the prepared formulations by performing stability studies according to ICH guidelines. Rofecoxib is used as a drug in present study because it is insoluble in water (Sifton DW *et al.*, 2002). It is a suitable drug for preparing suspensions. Rofecoxib is 4-[4-methylsulfonyl phenyl]3-phenyl-2(5H)furanone (Budavari S, 2001) Rofecoxib is comparatively a new non-steroidal anti-inflammatory drug ( Jacson LM *et al.*, 2000) which is selective Cyclooxygenase-2 (COX-2) inhibitor (Bombardier, 2001). COX-2 inhibitors were brought to the market as a safer alternative to traditional NSAIDs because of reduced incidence of side effects (Stempak D *et al.*, 2002). It comparatively exhibits lower incidence of symptomatic gastroduodenal ulcer complications than other NSAIDs (Langman MJ *et al.*, 1999). It is used in the treatment of osteoarthritis, acute pain, rheumatoid arthritis (Matheson AJ *et al.*, 2001), post-operative dental pain and primary dysmenorrhoea (Sifton DW *et al.*, 2002).

## MATERIALS AND METHODS

Rofecoxib, obtained as gift sample from Unichem Laboratories, Mumbai, and DOSS, Sodium alginate (Low viscosity), Xanthan gum, Methyl paraben Sodium, Propyl paraben sodium, S.L.S. (Sodium Lauryl Sulphate) and Sarbitol procured from Loba chemie Mumbai, Veegum, HI Media, Mumbai, Potassium dihydrogen phosphate, Sodium hydroxide pellets, Buffer Capsules pH4 & pH9.2, Acetone, Merck. Calcium Chloride dehydrate, S.D. Fine Chemicals, Mumbai, Aluminum Chloride, Qualigons Fine Chemicals.

### 1. Preparation

Suspensions containing 50 mg of Rofecoxib in 5ml. were prepared; In 100 ml of purified water, the required amount of surfactant/polymer/clay was added and kept overnight for proper hydration. These respective solutions were used as the vehicle in the preparation of the suspension. Accurately weighted quantity of rofecoxib was distributed into about ¾ th of vehicle the required

quantity of sorbitol was added and kept aside for 4 hrs for proper wetting. The slurry concentrate of the drug was mixed gently for 15 min. Calculated amount of 10% solution of calcium Chloride was added gradually to the uniformly distributed drug to achieve an optimum flocculation. Other ingredients like methylparaben sodium and propylparaben sodium were added and finally the volume was made up with the vehicle. Respective control suspensions were prepared similarly omitting the electrolyte. Purified water without any flocculating agent was used as the vehicle in the preparation of suspension F1.

### 2. Stability Studies

There are many dimensions of a suspension dosage form that are indicative of its quality, stability acceptance and performance. The effect of natural ageing on the stability of the prepared suspensions was studied. The formulated suspensions were evaluated at different time intervals for the following parameters.

#### Sedimentation Volume

The sedimentation volume (Sprowls *et al.*, 1974), ratio of the ultimate height ( $H_u$ ) of the sediment to the initial height ( $H_o$ ) of the suspension (i.e.  $H_u/H_o$ ) was calculated.

$$F = \frac{H_u}{H_o}$$

For each cycle the suspensions were transferred to 50ml stoppered measuring jars and were stored at room temperature ( $27 \pm 1^\circ\text{C}$ ). The volume of sediment formed was noted at 0, 1, 6, 12 & 24 hours interval of time.

#### Degree of flocculation

The Degree of flocculation ( $\beta$ ), which is the ratio of  $F$  to  $F_\infty$  ( $\beta = F/F_\infty$ ) is calculated from the sedimentation analysis of the suspensions, where  $f$  is the sedimentation volume of the flocculated suspension and  $F_\infty$  is the sedimentation volume of the deflocculated suspension.

#### Redispersibility

The suspension containing bottles were held up right between the fingers and rotated clockwise upside down through  $180^\circ$  in a semicircle path and back in the anti-clock wise direction. This process was repeated continuously until the sediment was completely redispersed. Number of such cycles to complete redispersibility was noted.

#### Particle size measurement

Size of rofecoxib particles in suspensions was measured by optical microscopy at 100X ( $10 \times 10$ ) magnification. The eye-piece micrometer was calibrated using a stage micrometer of American optical company, New York. Average particle size and standard deviation of 100 particles was determined.

#### pH measurement

The pH of the prepared suspensions was measured by using ELICO INDIA pH ANALYSER (Model LI612).

#### Viscosity Measurement

The viscosity of the suspensions prepared was measured by Brookfield viscometer (Model: DV-I+) at

100 rpm by using spindle no. 1.

**Drug content estimation**

Rofecoxib content was estimated by measuring the absorbance at 237nm using ELICO SL-159 UV-visible spectrophotometer against blank prepared from respective suspension without drug. The method obeyed beer’s Law in the concentration range of 2-30µg/ml. All the suspensions were again analysed periodically for Rofecoxib content during storage period.

**Dissolution Studies**

The dissolution rate of rofecoxib from various prepared suspensions was studied on Tab Machines, six stage digital dissolution rate test apparatus USP XXI using 900ml of pH 7.4 phosphate buffer with 0.5 S.L.S (Swati Rawat *et al.*, 2003) as dissolution medium with paddle at a rotational speed of 50 rpm and temperature 37±1<sup>0</sup>C. A sample of suspension equivalent to 50 mg of rofecoxib was employed in each test. The sample was introduced carefully at a fixed position near the bottom of the flask (about 2-2.5 cm) from the bottom, with syringe fitted with an extra-long tube. A 5ml aliquot of dissolution medium was withdrawn at different intervals of time (for about 60 min.) through a filter of size 0.45 µ suitably diluted and assayed spectro photometrically for rofecoxib content.

**RESULTS AND DISCUSSION**

Oral suspensions are useful dosage forms for administrating poorly soluble drugs. In the suspensions the drug particles exist in deflocculated or flocculated condition. Generally the drug particles will settle slowly and eventually form a hard cake in deflocculated

suspensions. Controlled flocculation approach is advocated to overcome this problem. In the present work ten aqueous oral suspensions of Rofecoxib were formulated with the objective of improving the physical stability by controlled flocculation approach. Sorbitol solution was used for wetting the drug powder, methyl paraben sodium and propyl paraben sodium were used as preservatives in all the formulations. Calcium chloride, aluminium chloride (RosenJ 1978, Jones RDC, 1970) (electrolytes), dioctyl sodium sulphosuccinate (Haines BA 1961, Hiestand EN, 1964) (DOSS, surfactant) sodium alginate, xanthan gum (Felmeister A *et al.*, 1973) magnesium aluminium silicate (Nash RA, 1965) (Veegum) were tried as flocculating agents. The suspension formulation code and the corresponding flocculating agents are given below.

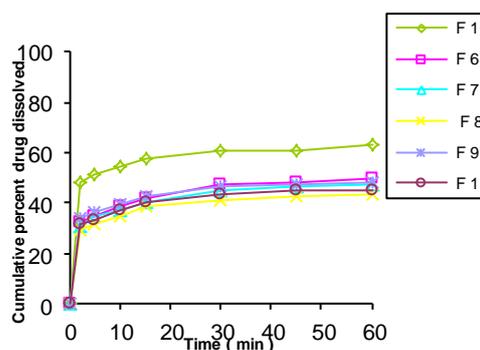
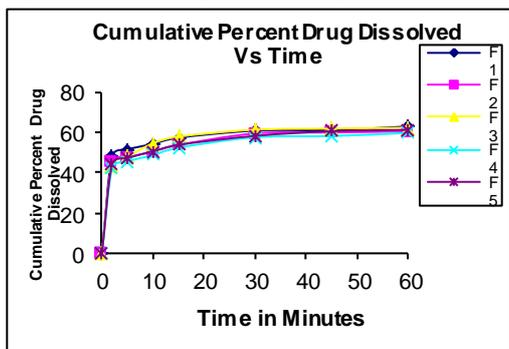
Formulation	Flocculating Agent
F <sub>1</sub>	Deflocculated Suspension (Control)
F <sub>2</sub>	Calcium chloride
F <sub>3</sub>	DOSS
F <sub>4</sub>	DOSS and Calcium Chloride
F <sub>5</sub>	Sodium alginate
F <sub>6</sub>	Sodium alginate and Calcium chloride
F <sub>7</sub>	Veegum
F <sub>8</sub>	Veegum and Calcium chloride
F <sub>9</sub>	Xanthan gum and Calcium chloride
F <sub>10</sub>	Xanthan gum and Aluminium chloride

The drug content was estimated in all the suspensions by UV spectrophotometric method and there was no chemical incompatibility was seen between the drug and the flocculating agents.

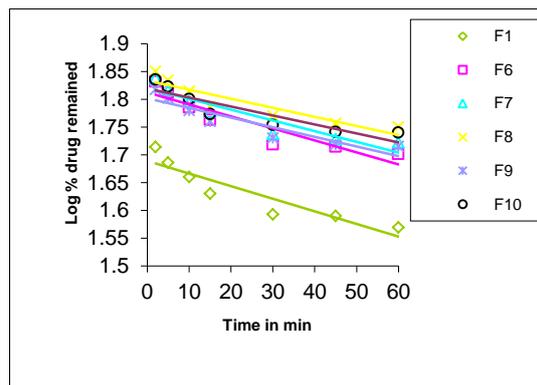
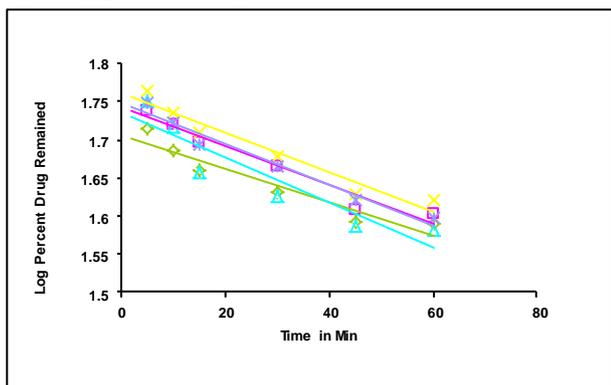
**Table.1 Comparative Analysis of Various Stability Parameters of Deflocculated and Flocculated Suspensions at 0 Month by Using Two - Sample - T – Test**

Sl. No.	Stability Parameter	De-flocculated suspensions A.V ± S.D.	Flocculated suspensions A.V ± S.D.	t-value
1	Assay	98.267±1.3597	101.23±6.1379	0.94270 NS
2	Average particle size	35.84±3.2375	37.376±4.4824	0.5626 NS
3	p <sup>H</sup>	8.9375±0.4966	8.547±2.0530	0.2613 NS
4	Viscosity	6.11±0.2521	8.39±1.4651	2.1675 NS
5	Sedimentation volume	0.023±0.0154	0.293±0.0822	6.4368 S
6	Degree of flocculation	2.875±1.9311	36.5±10.2794	6.4301 S
7	Redispersibility	9.5±4.7958	2.5±0.5773	2.9113 S
8	Dissolution (DE 45)	53.0075±2.9553	39.2±1.8738	25.139 S

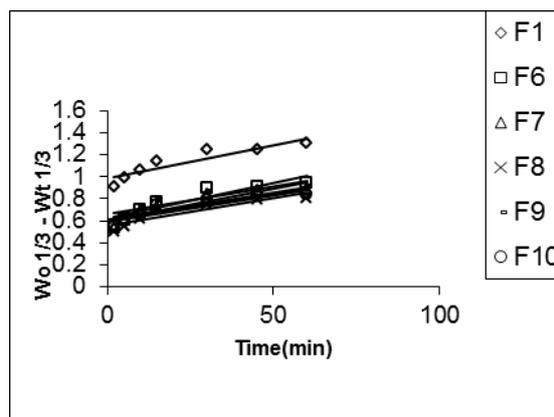
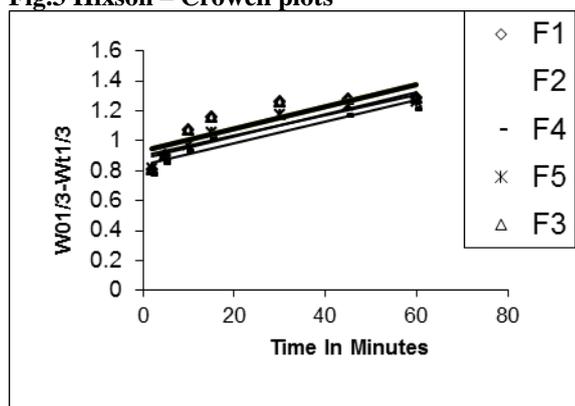
**Fig.1 Cumulative percent drug dissolved Vs Time**



**Fig.2 log percent drug remained Vs Time**



**Fig.3 Hixson – Crowell plots**



**Fig. 4 Rofecoxib flocculated(Veegum + Calcium Chloride) suspension and Deflocculated suspension (Control)**



The drug content was found to be uniform in all the formulations. The drug particles were found to be irregular in shape when observed under the microscope and the particle size was uniform in all the suspensions. It is not a variable factor and doesn't show any particular effect on the physical stability of different suspensions. The particle size distribution in the range of 32.58 to 42.19  $\mu\text{m}$ . All the suspensions showed low viscosity values between 4.08 to 12.2 cps, as no suspending agent was included in the formulation. The pH values were in the range of 6.98 to 9.90. Sedimentation volume (F) and the clarity of the supernatant liquid above the sediment are used as indices of flocculation. Flocculated systems

have high F values, whereas deflocculated systems settle to compact sediment and have low F values. Generally suspensions with low F values are difficult to redisperse. Another parameter for evaluating flocculation in a suspension is the degree of flocculation  $\beta$ . A flocculated suspension is characterized by large  $\beta$  value. Conversely a suspension containing highly condensed sediment will have small  $\beta$  value. The lower limiting value of  $\beta$  is 1, under such conditions there is no flocculation. Basing on the above criteria formulations F<sub>2</sub>, F<sub>3</sub>, F<sub>4</sub>, F<sub>5</sub> and F<sub>1</sub> (Control) were categorized as deflocculated suspensions and formulations F<sub>6</sub>, F<sub>7</sub>, F<sub>8</sub> and F<sub>10</sub> as flocculated respectively. In suspensions F<sub>6</sub>, F<sub>7</sub>, F<sub>8</sub>, and F<sub>10</sub>, high a sedimentation volume was seen compared to control F<sub>1</sub>, there was negligible improvement in sedimentation volume of F<sub>2</sub>, F<sub>3</sub>, F<sub>4</sub> and F<sub>5</sub>. The sedimentation volume of different deflocculated suspensions in the decreasing order was F<sub>4</sub> > F<sub>2</sub> > F<sub>3</sub> > F<sub>5</sub> / F<sub>1</sub>. The sedimentation volume of the flocculated suspensions in the decreasing order was F<sub>8</sub> > F<sub>10</sub> > F<sub>7</sub> > F<sub>6</sub>. Relatively more cycles 12, 6, 15, 5. Were required for complete redispersion of the drug in the first group of suspensions, i.e. F<sub>4</sub>, F<sub>2</sub>, F<sub>3</sub>, F<sub>5</sub> (deflocculated group), however, only to 2,2,3,3 cycles were required for redispersion formulations, i.e. F<sub>8</sub>, F<sub>10</sub>, F<sub>7</sub> and F<sub>6</sub> (flocculated group). The degree of flocculation of suspensions It is decreased in the order of F<sub>8</sub> > F<sub>10</sub> > F<sub>7</sub> > F<sub>6</sub> in the flocculated group and F<sub>4</sub> > F<sub>2</sub> > F<sub>3</sub> > F<sub>5</sub> in deflocculated group. In the case of suspension F<sub>9</sub>, with Xanthan gum and calcium chloride, no clear supernatant was obtained indicating the flocculation had not taken place. Physical incompatibility between Xanthan gum

and calcium chloride (Raymond C Rowe *et al.*, 2003) was also observed. The stability evaluation parameters of deflocculated group and flocculated group were compared by two sample t-test and the results are shown in Table.1. There was no significant difference between suspensions of deflocculated group and flocculated group with respect to assay, average particle size,  $p^H$  and viscosity. Flocculation imparted a structure to the suspensions with virtually no increase in viscosity. Significant difference was observed between suspensions of deflocculated group and flocculated group with respect to sedimentation volume, degree of flocculation, redispersibility and dissolution efficiency ( $DE_{45}$ ) values. The Zeta potentials of drug particles in  $F_1$ ,  $F_2$ ,  $F_3$  indicated that the addition of calcium chloride (or) DOSS did not result in large charge neutralization. However, low charge neutralization was seen, which could be the reason for slight increase in sedimentation volume. No correlation ( $r = 0.2898$ ) was observed between the Zeta potential and corresponding sedimentation volume. Polymers (Veegum, Xanthangum, and Sodium alginate) were found to act as flocculating agents in the formulation of Rofecoxib oral suspensions. Veegum produced the highest degree of flocculation resulting in improved physical stability. Sodium alginate + Calcium Chloride, Veegum + Calcium Chloride systems (Polymer + electrolyte) exhibited better flocculation and physical stability than the individual polymers. Suspension  $F_{10}$  containing Xanthan gum + Aluminium Chloride also produced, high degree of flocculation. The possible mechanism of flocculation by polymers, may be predominated by due to bridging. The linear branched chain molecules of the polymer could form gel like network within the system and become adsorbed onto the surface of the dispersed drug particles thus holding them in a flocculated state through polymer bridging. (Billany Michall, Aulton ME, 2002; Hiestand E, 1964; NashRA, 1965). Although Aluminium Chloride was found to be more efficient flocculating agent in the presence of Xanthan gum trivalent ions are less widely used than mono (or) divalent electrolytes because they are generally more toxic (Billany Michall, 2002). The dissolution profiles of Rofecoxib from the prepared suspensions were graphically represented (Fig.1 to 6). Three types of graphs were developed from the dissolution data, as mentioned below.

1. Cumulative percent dissolved Vs. Time graphs
2. Log % remained Vs. Time graphs,
3.  $W_0^{1/3} - W_t^{1/3}$  Vs. Time graphs

The cumulative percent of drug dissolved vs time graphs had shown that the percentage drug dissolved increased with respect to time. The graphs showed a steep rise in the first two minutes. This initial upsurge in dissolution might be due to large surface area of the fine drug particles immediately exposed to the dissolution medium. The dissolution profiles of Rofecoxib from the formulations do not fit adequately to the first order kinetic model ( $r$  values between -0.8561 to -0.94496), though close to the first order kinetics. However, it was found that the drug dissolution followed a biphasic dissolution profile consisting of an initial (0-2 min.)

upsurge followed by (2-60 min.) a near first order kinetics. In the case of the dissolution of Rofecoxib suspensions, ( $F_5, F_7, F_4, F_6, F_9, F_2, F_1, F_8, F_{10}$ ) obeyed and the rest did not obey properly Hixson-Crowell's cube-root dissolution rate equation. The correlation coefficients between  $(W_0^{1/3} - W_t^{1/3})$  and time values were in the range of 0.8492 to 0.94041 with various formulations.

Dissolution efficiency  $DE$  values were calculated by the method suggested by Khan (Khan KA, 1975) from the cumulative percent dissolved vs time graphs. Formulation  $F_3$  showed the highest dissolution efficiency. The dissolution efficiency of different formulations in the decreasing order is  $F_3 > F_4 > F_5 > F_1 > F_2 > F_6 > F_9 > F_7 > F_{10} > F_8$ . The cumulative percent drug dissolved and the dissolution efficiency values were decreasing with increasing degree of flocculation. Hence correlation coefficient was calculated to understand the relation between the two parameters. The values of correlation coefficients -0.98691/ -0.987/ -0.94487, indicated a negative correlation between the degree of flocculation and percent drug dissolved in 30 min/percent drug dissolved in 60 min and  $DE_{45}$  values respectively.

All the prepared suspensions were subjected to stability testing by exposing them to  $40^\circ\text{C} \pm 2^\circ\text{C} / 75\% \text{RH} \pm 5\% \text{RH}$  up to 6 months in a humidity chamber. The physical stability parameters were analysed at 0,2,4 and 6 months interval. The artificial ageing induced changes in the physico - chemical properties of the suspensions at various levels. A brownish discoloration of the supernatant (colourless to brown colour) was observed in suspension  $F_6$  containing Sodium alginate and calcium chloride. Large drug particles were observed in suspension  $F_4$  (DOSS + Calcium Chloride) after ageing which might be due to the formation of agglomerated (or) coagulated irreversible systems (Robert A Nash, 2002). Zapata et al have reported the formation of visible aggregates in pharmaceutical suspensions after freeze - thaw testing (Zopata MI *et al.*, 1984). The change in the average particle size on ageing is indicating that there was an increase. The particle growth was not uniform, rather it was more in the deflocculated suspensions compared to flocculated suspensions. The effect of ageing on pH and apparent viscosity indicating there was no change in viscosity, but a slight changing the pH. sedimentation behaviour/pattern and redispersibility, with age in general there was decrease in sedimentation volume with poor redispersibility was seen after ageing. Among all the suspensions flocculated suspension  $F_8$  (Veegum + Calcium Chloride) system found to retain the initial physicochemical properties with minimal affect after stability testing. Hence formulation  $F_8$  might be considered as the most stable suspension in the present work. The dissolution data after ageing it was noted that, in general there was retardation in dissolution with age in all the suspensions. In the case of deflocculated suspensions, there was a drastic retardation, however in the case of flocculated suspensions the retardation was lesser. The retardation in dissolution rate may be due to caking tendency of the sediment in deflocculated suspensions. After/ following the accelerated stability testing, significant increase in number of cycles required

for uniform redispersion and decrease in sedimentation volume also indicated cake formation in deflocculated suspensions. No cake formation was observed with flocculated suspension after stability testing. Controlled flocculation seems to be a useful approach for the improvement of physical stability of rofecoxib suspensions.

Cake formation is an important manifestation of physical instability of suspensions. Caking is defined as the formation of non-redispersible sediment within a suspension system (Nagin K. Patel *et al.*, 1987). The major causes of caking are crystal bridging and closed aggregate (Coagule) formation. In crystal bridging, particle surface crystal growth occurs on two (or) more particles simultaneously and results in the formation of crystal linked particles, ultimately leading to the formation of highly linked sediment akin to concrete (or) plaster. Suspensions of the dispersed type tend to cake easily, owing to the compact sedimentation that occurs when the particles settle.

Caking can also occur by extensive closed aggregate (Coagule) formation, although the mechanism of non redispersibility is different in that crystal bridging is not involved. A sedimented, highly coagulated suspension tends to form large coagules as the surface films present on coagulated particles cause the "filmed" particles to cling to each other. Although crystal growth may not occur upon sedimentation because of the presence of the surface films, the end result of a film-bonded sediment that cannot be redispersed is often observed for coagulated suspensions. An In-depth knowledge of caking mechanism is necessary for successful formulation of pharmaceutical suspensions.

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## CONCLUSION

Rofecoxib oral suspensions were formulated by using optimum concentrations of the flocculating agents in order to maximize sedimentation volume. The suspensions were exposed to ICH accelerated storage conditions i.e.  $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \text{RH} \pm 5\% \text{RH}$  upto 6 months and the physical stability parameters were analysed at regular intervals of time. The highest degree of flocculation was achieved with suspensions containing Veegum + Calcium Chloride system ( F<sub>8</sub> ) and Xanthan gum + Aluminium Chloride system ( F<sub>10</sub> ). Polymer bridging appears to be the most efficient approach in the formulation of Rofecoxib flocculated suspensions. The combination of polymer and electrolyte produced better flocculation than the individual agents. The drug dissolution from the suspensions followed a biphasic profile consisting of an initial upsurge followed by near first order kinetics. An inverse relationship was observed between degree of flocculation and percent drug dissolved in 30 min /D.E. From the stability studies it was found that the suspension containing Veegum + Calcium Chloride ( F<sub>8</sub> ) was the best formulation among all the suspensions prepared. Further studies are required to develop a set of guidelines in order to understand the effect of ageing on the physiochemical properties of pharmaceutical suspensions.

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