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Inclusion Complex of Solid State Aspirin with Fulvic Acid: Dissolution, Permeability, Stability and Preliminary Pharmacological Studies

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Abstract: This study was performed on the possibility of novel complexing agent/bioavailability enhancer in the form of complexation of aspirin with fulvic acid. Solid complexes of aspirin-fulvic acid prepared by solvent evaporation, freeze drying and spray drying methods. These complexes were characterized by using differential scanning calorimetry, fourier transform infrared spectroscopy, powder X-ray diffractometry and scanning electron microscopy. In addition, the influences of the fulvic acid on the dissolution, permeation, stability and pharmacodynamics profile of the complexes were studied. *In vitro* dissolution studies confirmed the successful complexation by the spray drying method in a molar ratio of 1:1. The prepared optimized complex showed an improvement in stability and permeability (8 times as compared to pure drug). A significant ($p < 0.05$) anti-inflammatory action of the treatment of optimized spray dried (1:1) aspirin complex with fulvic acid was evidenced by inhibition of rat paw edema and anti-ulcerogenic action was measured by lowest score of ulcer index (0.48 ± 0.08) with significant reduction in ulceration as compared to pure drug. Fulvic acid appears to be beneficial to overcome the problem of stability and bioavailability of aspirin. A highly significant anti-inflammatory and anti-ulcerogenic action was observed by the treatment of optimized complex. Technology has been developed which can be used for improvement formulation of aspirin.

Key words: Aspirin, fulvic acid, characterization, stability, bioavailability

INTRODUCTION

Shilajit, a wonder medicine used in the indigenous system of treatment by Vaidis and Hakims. It is neither a plant nor an animal origin; it is a mineral pitch that comes out from the rocks of the Himalayas during summer season (Chopra *et al.*, 1958; Ghosal, 1992; Frawley and Lad, 2001; Ghosal, 2006; Agarwal *et al.*, 2007a). It is also found in many other mountain ranges of the world, e.g., Afghanistan (Hindukush), Australia (Northern Pollock Ranges) and in the former USSR (Tien-Shan, Pamir, Caucasus, Ural), where it is collected in small quantities from steep rock faces at altitudes between 1000 and 5000 m (Ghosal, 2006). Shilajit has been reported to contain a number of components. The major portion is classified into humic and non-humic substances. Humic acid and Fulvic acid are the two major components of humic substances found in shilajit (Ghosal, 2006; Agarwal *et al.*, 2010).

Fulvic acids have relatively open, flexible structure punctured by voids (micropores) of different diameters (Ghosal, 2003; Agarwal *et al.*, 2008). These compounds

were, presumably, loosely held in the core structure of shilajit (Anwer *et al.*, 2010a, b). The plant secondary metabolites which are trapped in the internal voids of fulvic acids are spared from and become resistant to common chemical and biological decomposition (Agarwal *et al.*, 2007b; Agarwal *et al.*, 2008). Taking a clue on this point we started to investigate the potential of fulvic acid as a novel complexing agent in order to increase the stability and pharmacodynamic profile of aspirin. These fulvic acids provide the protective layer around aspirin in which water is excluded as much as possible and reduce the decomposition (Ghosal, 2003; Anwer *et al.*, 2010a, b).

Aspirin is the most widely used drug across the world. It has excellent medicinal value in its health protection function such as analgesic, anti-inflammatory, antipyretic and antithrombotic and has received more and more attention (Choi, 1989; Vane and Botting, 2003). These actions arise due to decreased production of prostaglandin and thromboxanes (Vane and Botting, 2003). The aspirin molecule has a carboxyl group and an ester group. The ester group can be easily hydrolyzed

which reduces the medicinal efficacy and has gastrointestinal side effects on humans (Connors *et al.*, 1986).

In this study, investigations were performed on the possibility of complexation of aspirin with fulvic acid for improving the dissolution rate, permeability, stability and pharmacodynamic profile, thereby increasing the bioavailability and therapeutic efficacy.

MATERIALS AND METHODS

Chemicals: Shilajit was kindly supplied by Dabur Research Foundation, India and aspirin was purchased from sigma-Aldrich, Germany. All other chemical were of analytical reagent grade.

Preparation of inclusion complexes: Complexes of Aspirin-fulvic acid in the molar ratio of 1:0.5, 1:1 and 1:2 were prepared by using solvent evaporation (rota evaporator), freeze drying (Lyophilizer) and spray drying (mini spray dryer) methods (Anwer *et al.*, 2010a).

Solvent evaporation (SE): Complexes were prepared by dissolving the required quantity of aspirin in 50 mL of chloroform and fulvic acid in 100 mL of water. The fulvic acid solution was then added to aspirin solution with stirring and the solution was sonicated in the ultrasonicator bath for 2 h. The solution thus obtained was dried in a rotary evaporator under reduced pressure on boiling water bath. The complex was then dried in oven, collected and passed through sieve No. 60. It was stored in vacuum desiccator till use.

Freeze drying (FD): Aspirin and fulvic acid were dissolved in double distilled water and sonicated for 2 h to get a clear solution. The solution was frozen in ultra freezer by keeping for 24 h and freeze dried over 12 h in Lyph-lock apparatus. The resulting amorphous powder is powdered in glass mortar and pestle and pass through 100-mesh sieve to obtain a uniform size fine powder.

Spray drying (SD): Complexes of Aspirin and fulvic were prepared by dissolving the required quantity of aspirin and fulvic acid in 100 mL of ethanol (95%). Solution was sonicated in the ultrasonicator bath for 2 h. The solution thus obtained was then spray dried using the following optimized condition-flow rate: 1.6 mL min⁻¹, outlet temperature: 135°C, atomizing air pressure: 3 kg cm⁻². The yield of the product was found to be 55% of the initial content (Moyano *et al.*, 1997).

Characterization of complexes: The complexes were characterized by using Differential Scanning Calorimetry

(DSC), X-Ray Diffraction (XRD), Fourier transform infra red spectroscopy (FT-IR) and Scanning Electron Microscopy (SEM) methods (Anwer *et al.*, 2010a).

Differential scanning calorimetry (DSC): Thermal behavior of aspirin and fulvic acid and their complexes were examined by using a Perkin Elmer Pyris 6 DSC. Inert nitrogen gas was used as carrier gas and the DSC analysis was carried out at a heating rate of 10°C min⁻¹ and a nitrogen gas flow rate of 20 mL min⁻¹. The sample size was 1 mg and examinations were made in the temperature intervals between 50 and 400°C.

Fourier transforms infra-red spectroscopy (FT-IR): The FT-IR spectra of aspirin, fulvic acid and inclusion complexes of aspirin were recorded on the Win-IRrez (Bio-Rad) using the potassium bromide (KBr) disc technique.

Sample equivalent to 2 mg of aspirin was mixed with potassium bromide (about 100 mg) using a clean glass pestle and mortar and compressed to get a pellet. Base line was corrected and scanning was done from 4000 to 400 cm⁻¹.

X-ray diffraction of solid complexes (X-RD): X-ray diffraction of samples was obtained by using X-ray diffractometer (PW 1830, Phillips, Japan). The scanning rate was 4° min⁻¹. The voltage/current used was 30 kV/ 25 mA and the target/filter (monochromator) was copper.

Scanning electron microscopy (SEM): SEM of samples were performed using Jeol scanning Microscope JSM-840 with a 10 kV accelerating voltage. The surface of the samples for SEM was previously made electrically conductive in a sputtering apparatus (Fine coat ion sputter JFC-1100) by evaporation of gold. A magnification of 1500 was used.

Release study of aspirin from their complexes: The dissolution rate studies were performed according to the USP XXVI rotating paddle type method. The sample corresponding to 100 mg of aspirin were placed in hard gelatin capsules. Dissolution medium was acetate buffer (pH 4.5). The stirring speed was 50 rpm and temperature 37±0.5°C. About 5 mL samples were withdrawn at a settled time interval using a syringe and analyzed by HPLC method.

Drug permeation study across rat everted gut sac: In order to study the effect of complexation on the intestinal permeability aspirin-fulvic acid spray dried complex (1: 1) was compared with aspirin powder alone by the rat everted gut sac technique (Barthe *et al.*, 1998). For the study, rat everted intestinal sac of about 5 cm were

prepared and filled with about 3.0 mL of tissue culture medium TC 199. The sacs were placed in tubes containing 25 mL of TC 199 medium in which excess (about 50 mg equivalent of aspirin) of either aspirin alone or optimized complexes of fulvic acid and HP- β -CD had been dissolved. The tubes were maintained in a shaking water bath at 37°C at a speed of 50 rpm. Samples were withdrawn from the mucosal and serosal side at the start and after 2 h. The samples were centrifuged for 5 min at 2000 rpm, filtered through 0.22 μ m membrane filter and analyzed by HPLC method.

Accelerated stability studies for shelf life determination:

Optimized complex of fulvic acid was packed in a laminated aluminum foil and stored at temperature of 40 \pm 2, 50 \pm 2 and 60 \pm 2°C for 120 days. Samples were withdrawn at intervals of 0, 30, 60, 90 and 120 days (Al-Gohary and Al-Kassas, 2000). The samples were analyzed for their drug content by HPLC analysis using the standard curve. The log of drug remaining was plotted against time. Slope of each line was obtained and degradation rate constant was calculated by the formula:

$$\text{Slope} = -\frac{K}{2.303}$$

where, K is the degradation rate constant.

The effect of temperature on the degradation was studied by plotting log K v/s 1/T.

Pharmacological studies

Anti-inflammatory studies: Anti-inflammatory activity was performed using carrageenan induced rat hind paw edema model. Wistar male albino rats, each weighing 150-200 g were divided into four different groups each containing 4 rats. Acute inflammation was produced by injecting 0.1 mL of 1% w/v carrageenan solution in the subplantar region of the rat right hind paw. Animals of group 1 served as control and received vehicle only (10 mL kg⁻¹ body weight of 1% CMC). Group 2 received pure drug aspirin suspended in 1% sodium carboxy methyl cellulose at dose of 100 mg kg⁻¹ and group 3 received optimized spray dried (1:1) complex of aspirin with fulvic acid suspended in 1% sodium carboxy methyl cellulose at dose equivalent to 100 mg kg⁻¹ aspirin 1 h prior to the carrageenan injection. The paw volume was measured at 0, 1, 2, 3 and 4 h after the injection of carrageenan by using digital plethysmometer. The paw is inserted into water in a clear acrylic cell, up to the mark. The water displacement produced by the immersion of paw in the measuring tube induced a change in the conductance, as measured between two platinum electrodes in the second tube. The plethysmometer's control unit measured these conductance changes and generated an output signal, accurate to 0.01 mL.

Pylorus ligated gastric ulceration: Male albino rats weighing between 140 and 170 g were selected for pyloric ligation ulcer model (Shay *et al.*, 1945). Rats were divided into five groups, each group consisting of five animals. Animals were fasted for 24 h. All groups are treated immediately after the pylorus ligation. Group 1 received 1% sodium carboxy methyl cellulose (1% Na-CMC), group 2 received pure drug aspirin suspended in 1% Na-CMC at dose of 100 mg kg⁻¹ and group 3 received optimized spray dried (1:1) complex of aspirin with fulvic acid suspended in 1% Na-CMC at dose equivalent to 100 mg kg⁻¹ aspirin. Animals were sacrificed 4 h later by an overdose of ether and the stomach was opened to collect the gastric contents. The stomach is removed and slightly inflated by injection of 1% formalin solution through esophageal junction. Then the stomach is maintained in 1% formalin solution for 10 min for fixation of the inner and outer layer of the gastric wall. The stomach is opened along the greater curvature and the length of lesions (dark blue areas against pale blue background) in the glandular portion is measured under a dissecting microscope (40x) provided with square grid (Takagi and Okabe, 1976).

RESULTS AND DISCUSSION

Characterization of complexes

Differential scanning calorimetry: DSC thermogram of aspirin as such in comparison to that of fulvic acid and the aspirin-fulvic acid complexes (ASA-FA) prepared by different technique in different molar ratios are shown in Fig. 1. The DSC thermogram of pure aspirin drug powder showed a sharp endotherm near 135°C which is indicative of its melting temperature (Anwer *et al.*, 2010b). Fulvic acid did not exhibit any sharp endothermic peak indicating that it does not have any defined melting point (Khanna *et al.*, 2008). Solvent evaporated ASA-FA complex in the molar ratio of 1:0.5 and 1:1 exhibited a sharp endothermic peak near 135°C. This indicates that aspirin is not complexed with fulvic acid which may be due to insufficient quantity of fulvic acid and the residual aspirin gives an endothermic peak near its melting point. However, complexes in the molar ratio 1:2 confirmed complete complexation as they did not show endothermic peak near melting point of drug. Lyophilized complex in the molar ratio 1:0.5 showed sharp endothermic peak at 135°C due to insufficient quantity of fulvic acid which results in incomplete entrapment of aspirin inside the cavity of fulvic acid. However, in 1:1 molar ratio complex, a less intense endothermic peak of drug was observed, confirming partial complexation. However, in the 1:2 molar ratios complete disappearance of endothermic peak of aspirin was observed, supporting complete complexation.

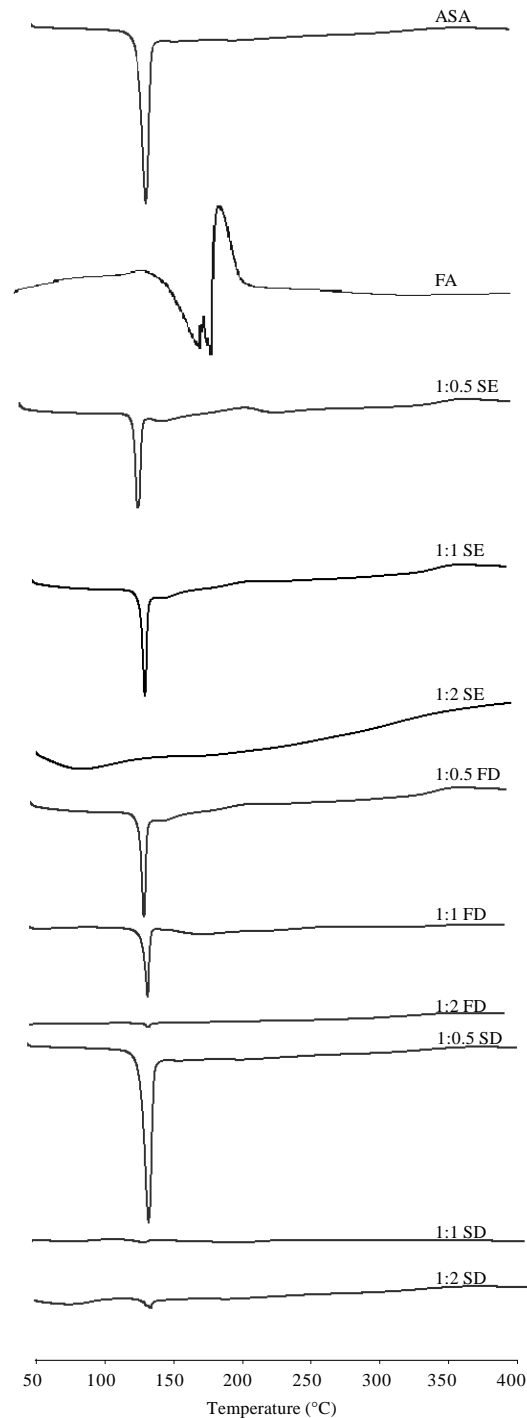


Fig. 1: Differential scanning calorimetry (DSC) thermogram of fulvic acid complexes prepared by different methods ASA: Aspirin, FA: Fulvic acid, 1:0.5 SE: 1:0.5 aspirin-fulvic acid complex solvent evaporation (SE), 1:1 SE: 1:1 aspirin-fulvic acid complex Solvent evaporation (SE), 1:2 SE: 1:2 aspirin-fulvic acid complex solvent evaporation (SE); 1:0.5 FD: 1:0.5 aspirin-fulvic acid complex freeze drying (FD), 1:1 FD: 1:1 aspirin-fulvic acid complex freeze drying (FD); 1:2 FD: 1:2 aspirin-fulvic acid complex freeze drying (FD); 1:0.5 SD: 1:0.5 aspirin-fulvic acid complex spray drying (SD), 1:1 SD: 1:1 aspirin-fulvic acid complex spray drying (SD), 1:2 SD: 1:2 aspirin-fulvic acid complex spray drying (SD)

Spray dried complex in the molar ratio 1:0.5 showed a sharp endothermic peak due to the fusion of aspirin crystal indicating no complexation. However, in the molar ratio 1:1 complex, complete absence of endothermic peak of aspirin was observed, revealing successful entrapment of drug inside the void of fulvic acid.

Fourier transforms infra-red spectroscopy: Characteristic peaks at $1,754\text{ cm}^{-1}$ (acetoxy C = O group stretching), $1,693\text{ cm}^{-1}$ (carboxyl C = O group stretching) and $1,606\text{ cm}^{-1}$ (C = C aromatic stretching) confirmed the presence of pure aspirin. Fulvic acid exhibited a broad band at about 3382 cm^{-1} which can be attributed to stretch of hydrogen-bonded OH group. A peak at 2930 cm^{-1} (stretch of aliphatic C-H) is present. Two bands were also observed in the region of 1613 cm^{-1} (Aromatic C-C double bond, H-bonded C-O of conjugated ketones) and 1411 cm^{-1} (O-H bending vibrations of alcohols or carboxylic acids). The band at 1081 cm^{-1} can be attributed to C-O stretching indicating the presence of polysaccharide or polysaccharide like compound (Schnitzer, 1972).

As we look on the FT-IR spectrum of inclusion complex (1:1), the acetoxy carbonyl at 1754 cm^{-1} was disappeared while carboxyl carbonyl band at 1692 cm^{-1} present. It suggested from the spectra that acetoxy carbonyl group of aspirin has been interacted with fulvic acid. The FT-IR spectra of freeze dried ASA-FA complex in the molar ratio 1:1 showed that the acetoxy carbonyl absorption band shifted to lower frequency at 1748 cm^{-1} with diminished peak. The absorption band at 1748 cm^{-1} could be assigned to the free acetoxy carbonyl stretching dispersed in fulvic acid. The FT-IR spectra of 1:2 freeze dried complex showed that absorption band at 1754 cm^{-1} (acetoxy C = O group stretching), 1693 cm^{-1} (Carboxyl C = O group stretching) completely disappeared, suggesting complete entrapment of aspirin inside the void of fulvic acid. The FT-IR spectra of spray dried ASA-FA complex in the molar ratio 1:1 showed that the acetoxy carbonyl absorption band and acetoxy carbonyl stretching band were completely disappeared, revealed complete complexation. The FT-IR spectra of 1:2 solvent evaporated complex showed that absorption bands at 1758 cm^{-1} (acetoxy C = O group stretching), 1690 cm^{-1} (Carboxyl C = O group stretching) present with very less intensity, confirming partial complexation (Fig. 2).

X-ray diffraction pattern: X-ray diffraction pattern of aspirin as such in comparison to that of fulvic acid and aspirin-fulvic acid complex prepared in different molar ratio are presented in Fig. 3. Aspirin-fulvic acid complex prepared by solvent evaporation in the molar ratio of 1:0.5

exhibited a partially crystalline nature as evident by the lack of some characteristic peaks of aspirin which were of reduced intensity. However, XRD pattern of complex in the molar ratio 1:1 and 1:2 exhibited amorphous nature as it does not show any intense peak of drug. Some peaks of fulvic acid could be observed. Freeze dried complex in the molar ratio 1:1 and 1:2 showed few intense peaks revealing its amorphous nature. This amorphous nature of the complex may be due to lyophilization. However, XRD pattern in the case of 1:1 spray dried complex showed complete disappearance of peaks demonstrating that complex formation has taken place between aspirin and fulvic acid (Patil and Patil 2012). However, complexes of 1:2 exhibited some intense peaks demonstrating partial complexation between drug and fulvic acid.

Scanning electron microscopy (SEM): Although, SEM is not conclusive for assessing the existence of a true inclusion compound in the solid state, it can be of some utility to prove the homogeneity of the solid phases. SEM of aspirin showed crystalline particles of regular size, indicating crystalline nature. Fulvic acid appears as fibrous material (Khanna, 2006). The photomicrographs of spray dried aspirin-fulvic (1:1) complex showed the typical morphology of preparations that is small size particles tending to aggregation, suggesting the existence of an amorphous product with the presence of a single component in the complex, thus suggesting maximum or complete complex formation (Fig. 4).

Release study of aspirin from their complexes: The release profile of aspirin-fulvic acid systems prepared by solvent evaporation and freeze drying method are shown in Fig. 5. The dissolution data indicated only 31.32% release was obtained with aspirin alone at 30 min and a maximum of 99.7% release was obtained from 1:1 spray dried fulvic acid complex in 25 min. The study clearly demonstrates that when aspirin is complexed with fulvic acid there is a significant increase in the dissolution rate of the drug i.e., aspirin complex.

Drug permeation study across rat everted gut sac: As seen from the Fig. 6, the permeation of aspirin from aspirin-fulvic acid complex (1:1) prepared by spray drying was found to be significantly higher (about 8 times) as compared to aspirin alone (Fig. 6).

Accelerated stability studies for shelf life determination: Optimized complex of fulvic acid was found to be more stable as compared to the pure aspirin. The plot of log % drug remaining Vs time is downward, indicating that the reaction is accelerating with time. Degradation of aspirin

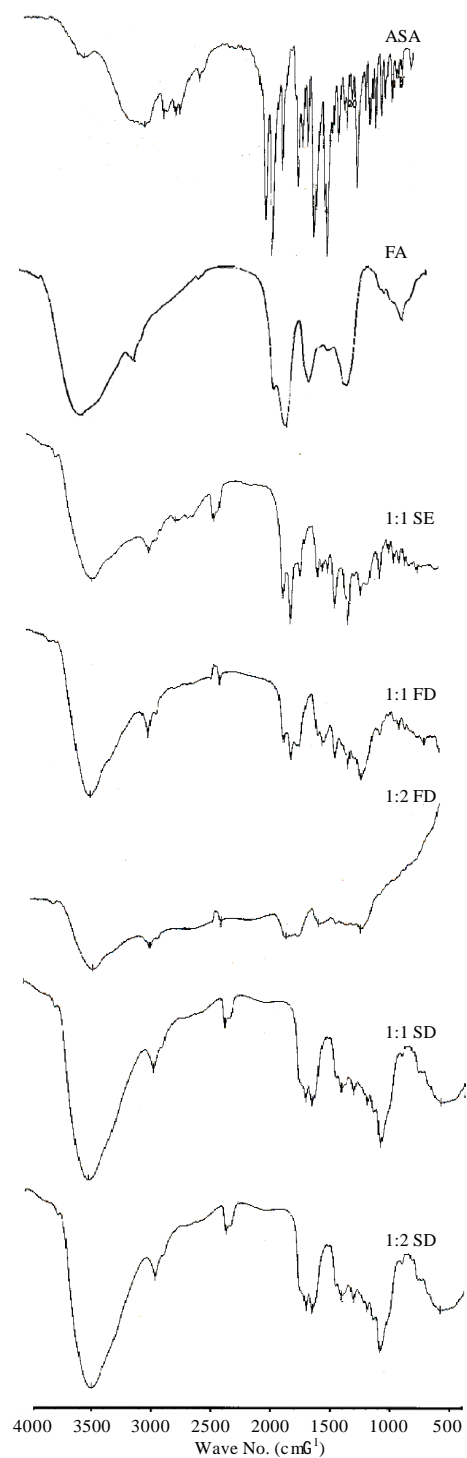


Fig. 2: Fourier transforms infra-red spectroscopy (FT-IR) spectra of fulvic acid complexes prepared by different methods, ASA: Aspirin, FA: Fulvic acid; 1:1 SE: 1:1 aspirin-fulvic acid complex Solvent evaporation (SE), 1:1 FD: 1:1 aspirin-fulvic acid complex freeze drying (FD), 1:2 FD: 1:2 aspirin-fulvic acid complex freeze drying (FD), 1:1 SD: 1:1 aspirin-fulvic acid complex spray drying (SD), 1:2 SD: 1:2 aspirin-fulvic acid complex spray drying (SD)

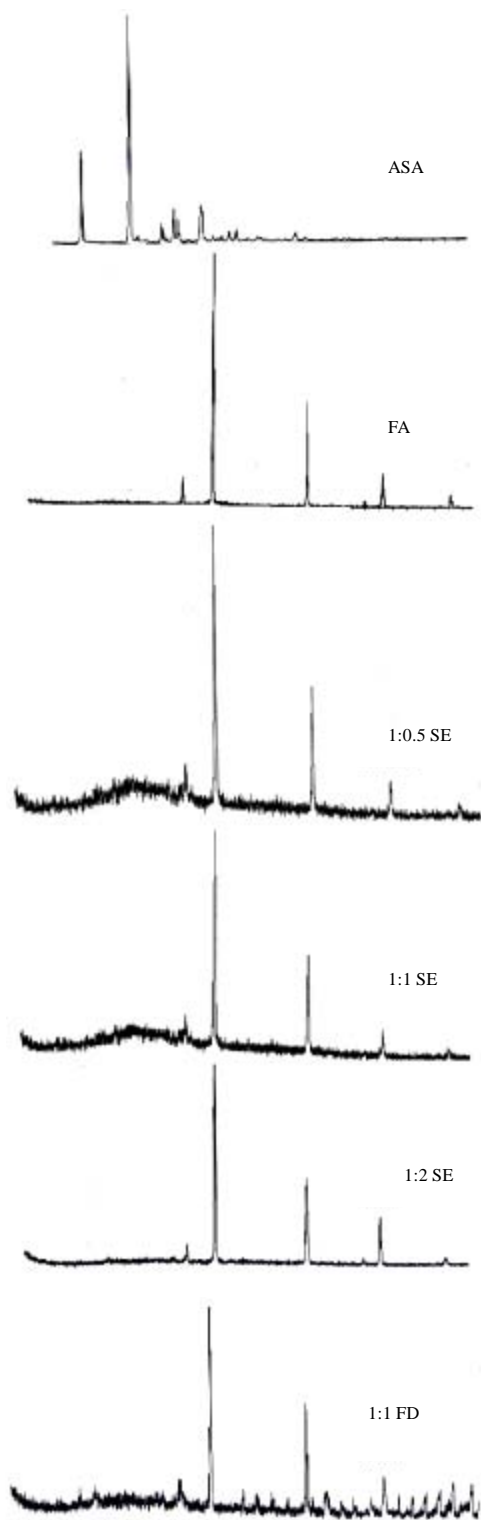


Fig. 3: Continue

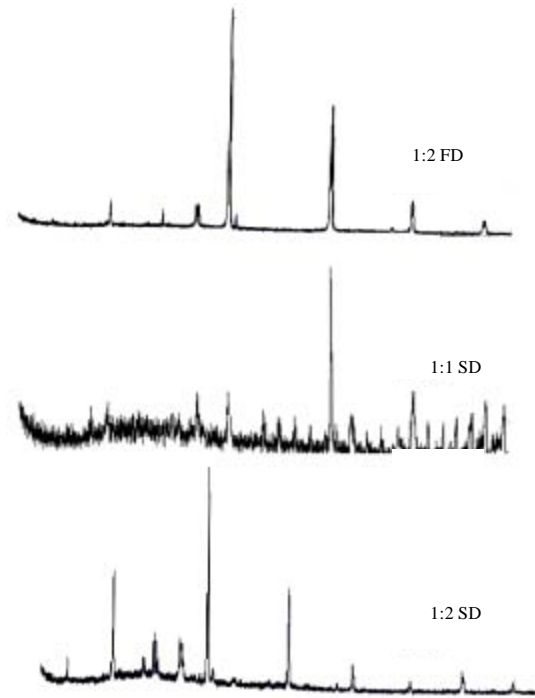


Fig. 3: X-Ray diffraction pattern (XRD) of fulvic acid complexes, ASA: Aspirin, FA: Fulvic acid, 1:0.5 SE: 1:0.5 aspirin-fulvic acid complex solvent evaporation (SE), 1:1 SE: 1:1 aspirin-fulvic acid complex Solvent evaporation (SE), 1:2 SE: 1:2 aspirin-fulvic acid complex solvent evaporation (SE), 1:1 FD: 1:1 aspirin-fulvic acid complex freeze drying (FD), 1:2 FD: 1:2 aspirin-fulvic acid complex freeze drying (FD), 1:1 SD: 1:1 aspirin-fulvic acid complex spray drying (SD), 1:2 SD: 1:2 aspirin-fulvic acid complex spray drying (SD)

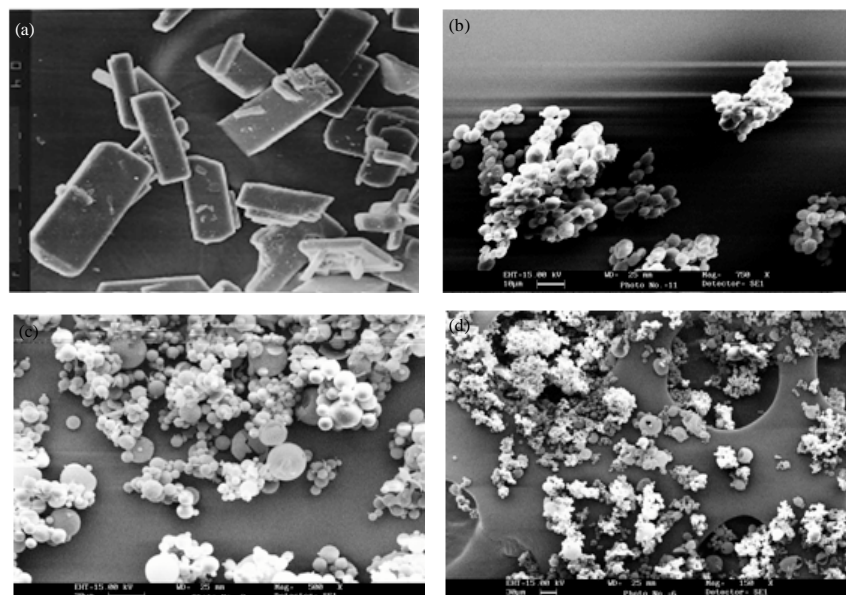


Fig. 4(a-d): Scanning electron microscopy (SEM) of aspirin, fulvic acid and optimized complex (a) Aspirin, (b) Fulvic acid and (c-d) Aspirin-fulvic acid (1:1) spray dried complex

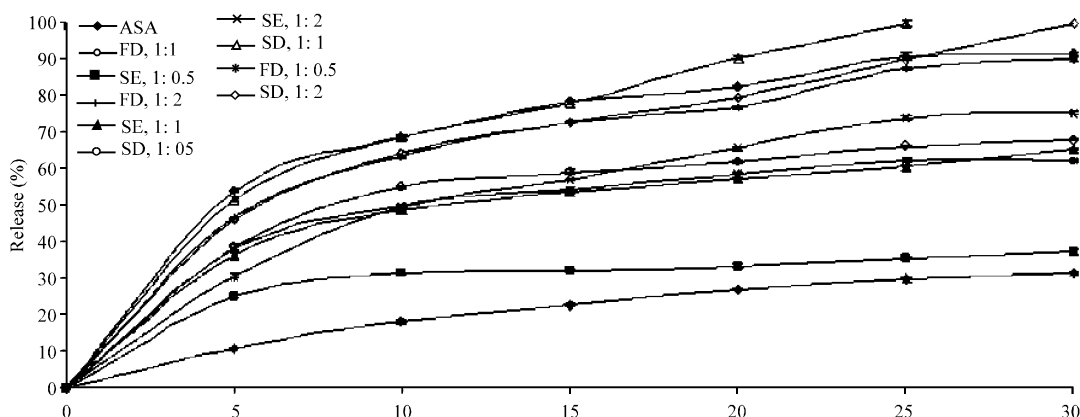


Fig. 5: Release profile of fulvic acid complexes in acetate buffer (pH 4.5), ASA: aspirin, FA: Fulvic acid, 1:0.5 SE: 1:0.5 aspirin-fulvic acid complex solvent evaporation (SE), 1:1 SE: 1:1 aspirin-fulvic acid complex solvent evaporation (SE), 1:2 SE: 1:2 aspirin-fulvic acid complex solvent evaporation (SE), 1:0.5 FD: 1:0.5 aspirin-fulvic acid complex freeze drying (FD), 1:1 FD: 1:1 aspirin-fulvic acid complex freeze drying (FD), 1:2 FD: 1:2 aspirin-fulvic acid complex freeze drying (FD), 1:0.5 SD: 1:0.5 aspirin-fulvic acid complex spray drying (SD), 1:1 SD: 1:1 aspirin-fulvic acid complex spray drying (SD) and 1:2 SD: 1:2 aspirin-fulvic acid complex spray drying (SD)

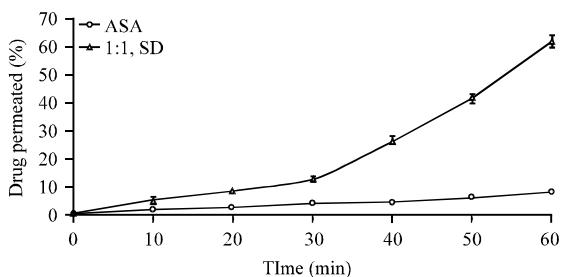


Fig. 6: Comparative permeation of aspirin and optimized complex across rat everted gut sac, ASA: Aspirin, 1:1, SD: 1:1 aspirin-fulvic acid complex spray drying

alone was rapid at higher temperature by the end of 120 days. The Arrhenius plots of the stability data at the three storage temperatures for the optimized complex of aspirin with fulvic acid, was presented in Fig 7. By extrapolation, the K_1 value at 25°C for the optimized complex of aspirin with fulvic acid was found to be 7.27×10^{-5} which corresponds to shelf-lives of 3.98 years (Fig. 8). The results revealed that the presence of the fulvic acid moieties as complexing agent has decreased the rate of aspirin decomposition and improved its shelf-life as compared to uncomplexed aspirin as compared to previous studies on aspirin-magaldrate double layer tablet (Al-Gohary and Al-Kassas 2000).

Pharmacological studies

Anti-inflammatory studie: The results of the anti-inflammatory effect of the aspirin and their optimized complexes on carrageenan-induced oedema in rat's right

Table 1: Inhibition of rat paw edema by aspirin and their optimized complex

Treatments	Inhibition/time (h) (%)			
	1	2	3	4
Aspirin	31.25	36.96	31.11	22.92
1:1 ASA-FA (SD)	62.50	63.04	93.33	35.42

1:1 ASA-FA (SD): 1:1 aspirin-fulvic acid complexes (spray drying)

hind paws are presented in Table 1. Pure aspirin caused an inflammation inhibition of 31, 37, 31 and 23 % while for spray dried complex of (1:1) aspirin with fulvic acid 62, 63, 93 and 35% inhibition were observed after 1, 2, 3 and 4 h, respectively. A significant ($p < 0.05$) anti-inflammatory action of the treatment of optimized spray dried complex of aspirin with fulvic acid (1:1) was evidenced by inhibition of rat paw edema as compared to aspirin alone. Previous anti-inflammatory action of shilajit (Acharya *et al.*, 1988) strongly support this study.

Pylorus ligated gastric ulceration: The spray dried complex prepared with fulvic acid gave the lowest score of ulcer; 0.48 ± 0.08 as compared to aspirin alone 1.12 ± 0.08 (Fig. 9). It is reported that crystals of aspirin being poorly soluble in gastric acid remain in contact with the stomach wall for a long period of time, resulting in a dangerously high local concentration. This leads to local irritation of the stomach wall and to ulceration. It is expected that in the complexed form, the drug will dissolve fast and show an accelerated absorption. Moreover, it will not come in direct contact with the stomach wall in crystalline state since until it is dissolved it remains encapsulated within the complex matrix. In a previous research the pharmacological actions of shilajit (Goel *et al.*, 1990) fulvic

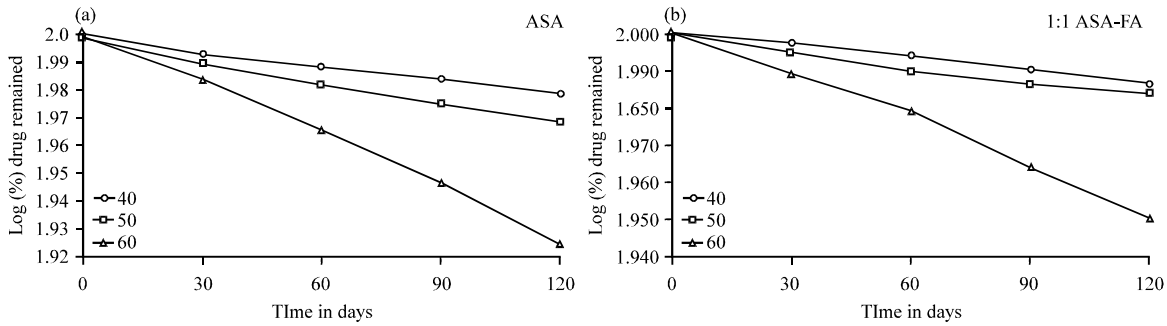


Fig. 7(a-b): Degradation of (a) Aspirin and (b) Spray dried aspirin-fulvic acid (1:1) complex, ASA: Aspirin; 1:1 ASA-FA: 1: 1 aspirin-fulvic acid complexes spray drying

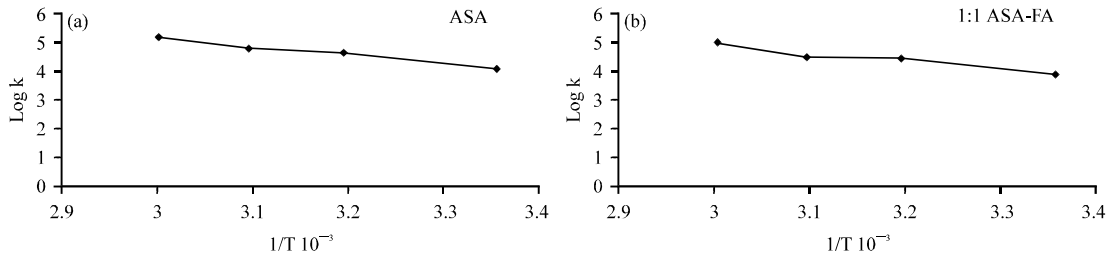


Fig. 8(a-b): Arrhenius plot for (a) Aspirin and (b) Spray dried (1:1) aspirin-fulvic acid complex, ASA: Aspirin; 1:1 ASA-FA: 1: 1 aspirin-fulvic acid complex spray drying

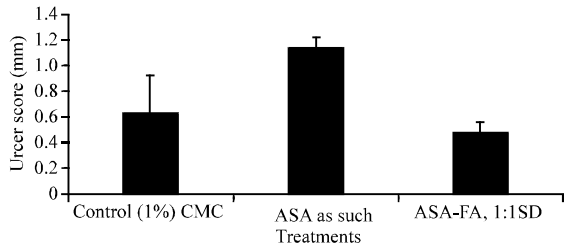


Fig. 9: Ulcer index after treatment, CMC: Carboxy methyl cellulose, ASA: Aspirin, ASA-FA, 1:1SD: 1: 1 aspirin-fulvic acid complexes spray drying

acid from shilajit, we indicated the possibility of antiulcerogenic properties of spray dried complex prepared with fulvic acid.

CONCLUSION

A novel complexing agent/bioavailability enhancer in the form of fulvic acid was investigated with successful enhancement in dissolution, permeability and stability of aspirin can be achieved through fulvic acid complexation. However, fulvic acid appears to be beneficial to overcome the problem of stability and bioavailability of aspirin. A highly significant anti-inflammatory and anti-ulcerogenic action was observed by the treatment of optimized complex. Technology has been developed which can be used for improvement formulation of aspirin.

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