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Research Article

# Design and *In-Vitro* Evaluation of Compressed Kollidon® SR Based Naproxen Sodium Microcapsule: Effect of Talc

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## Abstract

Naproxen sodium is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic antipyretic properties. In this research work, naproxen sodium was encapsulated by solvent-evaporation technique using kollidon® SR as coating polymeric material to prolong the therapeutic duration of the drug. Four different concentrations of talc were used as additives to see the changes in drug release pattern from the compressed microcapsules. Scanning Electron Microscopy (SEM) was applied to study size and surface morphology of prepared microcapsules. UV-spectrophotometric method was applied to calculate the drug loading efficiency and the performance of the prepared dosage form was evaluated in terms of in-vitro dissolution studies according to USP paddle method (type 2) in 400 ml in phosphate buffer (pH 6.8) for 8 hours at $37^0 \pm 5^0$ C temperature at 50 rpm. Release of naproxen sodium from the compressed microcapsules was found to follow hixon crowell mechanism ($R^2$=0.99). Hixon equation was used to calculate the release exponent value (n) which indicates the drug release behavior and the mean dissolution time T50% (MDT) for release rate. The surfaces of the microcapsules became smoother with the increase in talc amount and simultaneously decrease in drug release rate.

**Keywords:** Naproxen sodium, Kollidon® SR, microcapsule, emulsion solvent evaporation technique, MDT (Mean Dissolution Time)

## INTRODUCTION:

Naproxen sodium is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low $p^H$ and freely soluble in water at high $p^H$. The octanol/water partition coefficient of Naproxen sodium at $p^H$ 7.4 is 1.6 to 1.8. Naproxen sodium is freely soluble in water in neutral $p^H$. The elimination half-life of Naproxen is unchanged across products ranging from 12 to 17 hours. Steady-state levels of Naproxen are reached in 4 to 5 days, and the degree of Naproxen accumulation is consistent with this half-life. In this study water insoluble polyvinyl acetate and polyvinyl pyrrolidone (Povidone) based matrix polymer (Kollidon® SR) and talc were used for preparing microcapsules where kollidon® SR was used as rate controlling model polymer. The drug content in microcapsules is conventionally determined by extracting the drug or dissolving the dosage form in a solvent followed by quantification of the drug using an appropriate analytical technique. In this paper the effect of variable concentrations of talc on release of naproxen sodium from kollidon® SR based compressed microcapsules have been discussed.

## EXPERIMENTAL SECTION

Naproxen sodium was collected from rangs pharmaceuticals, Dhaka, Bangladesh, Kollidon® SR, from the regional office of BASF, Germany in Bangladesh, Liquid paraffin oil light, Pet-Ether (40-60) (MERCK, Germany), Span series (20 and 60) was collected from BDH Chemicals Ltd., England and Span 80 was collected form LOBA CHEMIE, India. Talc (Whittaker, Clark and Daniels Inc, USA). All other chemicals and ingredients were of analytical grade. Impact drill GSB 16RE (BOSCH, Germany), Stirrer (NIPUN, Bangladesh), UV-visible Spectrophotometer-1240(SHIMADZU, Japan) for absorbance determination, Scanning Electron Microscope (SEM) S-3400N (HITACHI, Japan), Sonicator (POWER SONIC 505, HWASHIN TECHNOLOGY CO., Seoul, Korea.), Tablet dissolution tester (USP Type III dissolution apparatus, VEEGO, India) for dissolution and Perkin-Elmer compressor machine for tablet compression were used in this study.

### Preparation of naproxen sodium microcapsules

Microcapsules were prepared by an emulsification solvent evaporation technique. Four batches of microcapsules were prepared with different concentration of talc (5%, 10%, 15% and 20% respectively).

**Table 1: Formulation, drug loading efficiency of different batches of microcapsules of naproxen sodium with kollidon® SR with Talc concentration change**

| Formulation | Material | | | | | | | | | Drug Loading | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NS (gm) | KS (gm) | Methanol (ml) | Talc | | | | Span 60 (gm) | Liquid paraffin (ml) | Theoretical loading (%) | Actual loading (%) | Loading Efficiency (%) |
| | | | | 5% (gm) | 10% (gm) | 15% (gm) | 20% (gm) | | | | | |
| F-1 | 4 | 4 | 10 | 0.2 | 0 | 0 | 0 | 0.1 | 100 | 50 | 43.11 | 57 |
| F-2 | 4 | 4 | 10 | 0 | 0.4 | 0 | 0 | 0.1 | 100 | 50 | 44.48 | 59 |
| F-3 | 4 | 4 | 10 | 0 | 0 | 0.6 | 0 | 0.1 | 100 | 50 | 54.90 | 73 |
| F-4 | 4 | 4 | 10 | 0 | 0 | 0 | 0.8 | 0.1 | 100 | 50 | 64.29 | 86 |

Kollidon® SR solution was prepared at a drug polymer ratio of 1:1 by dissolving kollidon® SR in methanol which acts as internal phase. 100 gm of liquid paraffin (heavy grade) was taken in properly washed and dried 500 ml glass beaker. Surfactant was added with the liquid paraffin and stirring (1000 rpm) was started. The stirring was continued for 5 minutes at 1000 rpm. The previously prepared Kollidon® SR-methanol-Naproxen Sodium solution was then poured into the liquid paraffin maintaining the speed at 1000 rpm for first 2 hours and at 3000 rpm for rest of the time. The stirring was continued until hard, uniform shaped microcapsules are formed. The container was then kept static to allow the microcapsules for settling down. Serial washing of microcapsules was carried out with n-hexane and cyclohexane alternatively followed by vacuum drying until a free flow bulk of microspheres is found. The prepared microcapsules were then sieved, weighed and transferred to glass vials and stored in desiccator. Then the formulations were named as F-1, F-2, F-3 and F-4 respectively as shown on table 1.

**Assay of microcapsules:**

A few mg of kollidon® SR microcapsules containing naproxen sodium was taken in a mortar and was triturated properly until fine powder was formed. 20 mg of fine powder was taken in a 100 ml volumetric flask with the help of a funnel. Few ml of phosphate buffer (pH 6.8) was added with the powdered microcapsule, sonicated for 30 minutes in a sonicator (POWER SONIC 505, HWASHIN TECHNOLOGY CO., Seoul, Korea) to make a clear solution and then finally was filtered. Absorbance value was determined using UV spectrophotometer (UV mini-1240, SHIMADZU CORP., Kyoto, Japan) at a wave length of 332 nm. Using the absorbance value, the amount of Naproxen sodium entrapped was determined with the help of standard curve.

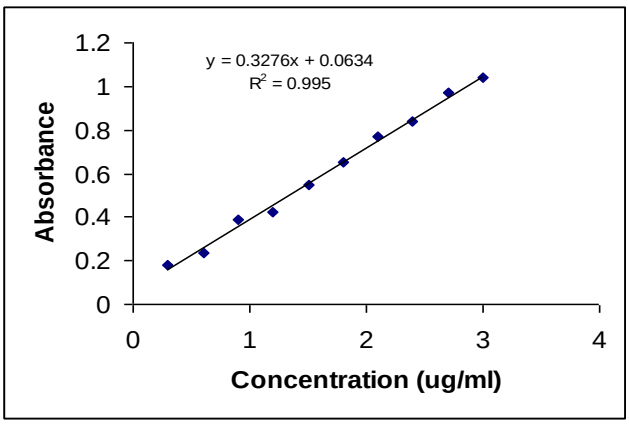



Figure 1: Standard Curve of Naproxen Sodium.

**Preparation of compressed microcapsule matrix tablet**

For each batch, 300 mg microcapsules or granules (150 mg microcapsules + 150 Ethocel 20 cps) were weighted in an electronic balance for the preparation of each tablet and compressed into the disk using "Perkin-Elmer" hydraulic press equipped with 13 mm faced punch and die set. The compression force and compression time were 5 ton and 30 seconds respectively.

**Table 2: Formulation of compressed microcapsules of naproxen sodium with kollidon® SR**

| Formulations | Amount of MC (mg) | Ethocel (mg) | Total weight (mg) |
|---|---|---|---|
| F-1 | 150 | 150 | 300 |
| F-2 | 150 | 150 | 300 |
| F-3 | 150 | 150 | 300 |
| F-4 | 150 | 150 | 300 |

*MC= Microcapsule

**In-vitro Dissolution Study of Naproxen Sodium from Kollidon® SR from compressed Microspheres:**

In-vitro dissolution study was performed in a Paddle type Dissolution Apparatus (USP Type III Dissolution Apparatus, VEEGO, INDIA). A fixed amount tablet (containing 150 mg of Naproxen sodium microspheres + 150 mg of Ethocel 20 cps) from each batch was calculated for dissolution purpose. Phosphate buffer solution of pH 6.8 was used as dissolution media, paddle speed was set at 50 rpm, and temperature was maintained fixed at 37ºC. The fixed amount of microsphere from each batch was weighed and transferred in each dissolution basket. The dissolution process was carried out for 8 hour and 10 ml dissolution sample from each batch was withdrawn at a predetermined intervals of 1 hour, 2 hour, 3 hour, 4 hour, 5 hour, 6 hour, 7 hour, 8 hour. Each and every time 10 ml dissolution sample was compensated by another fresh 10 ml phosphate buffer. Dissolution samples were withdrawn with the help of 0.45 µm sized disposable syringe filter (Microsart®, Hannover, Germany) and were kept

airtight in a screw cap test-tube. The dissolution samples were then analyzed spectrophotometrically in a UV-VIS spectrophotometer (UV mini-1240, SHIMADZU CORP., Kyoto, Japan) at a wavelength of 232 nm. The dissolution study for each batch was performed in triplicate.

**Release kinetics**

After linear transformation of dissolution curves, the results were tested with the following mathematical model.

- The Zero order equation assumes that drug release is constant:

$$M=M_0-K_0t \quad (I)$$

In this equation M is the amount of drug remaining undissolved at time t, $M_0$ is the

amount of drug undissolved at t = 0 and $K_0$ is the corresponding release rate constant

- Release behavior generally follows the following first order release equation:

$$\ln M = \ln M_0 - K_1t \quad (III)$$

Where M is the amount of drug undissolved at time t, $M_0$ is the amount of drug undissolved at t = 0 and $K_1$ is the corresponding release rate constant.

- A form of the Higuchi Square Root Law is given by equation:

$$Q = K_s \sqrt{t} \quad (II)$$

Where Q (Q = 100 - M) is the amount of drug dissolved at time t and $K_s$ is the corresponding rate constant.

- The Hixon - Crowell Cube Root Equation is:

$$\sqrt[3]{M} - \sqrt[3]{M_0} = K_c t \quad (IV)$$

Where $K_c$ is the cube root dissolution rate constant.

**Surface Morphology study with the help of Scanning Electron Microscope (SEM):**

Surface nature of the microspheres was examined with the help of Scanning Electron Microscope (S-3400N, Hitachi). The microspheres were dried completely before examination. SEM was done at different magnifications of 15.0 kv X 25 SE, 15.0 kv X 100 SE, 15.0 kv X 500 SE, 15.0 kv X 2.00k SE.

## RESULTS AND DISCUSSION

**Effect of concentration of Talc on the release of drug from compressed microcapsule**

Four different concentrations of talc for 5%, 10%, 15% and 20% were used for F-1, F-2, F-3 and F-4 formulations respectively. Drug loading efficiency was assumed 50% for each formulation. The data of loading efficiency of each batch is represented in table 1. From the zero order release, the figure 1 (a) depicts the release profile of naproxen sodium from compressed microcapsules with kollidon® SR with varying talc concentrations. Initial burst release as different for the each formulation. For F-1, F-2, F-3 and F-4 about 16.78%, 3.59%, 2.67% and 6.15% respectively. The burst release was observed after 2 hours. After the end of 8 hours of dissolution study, the approximate percent release of naproxen sodium for F-1, F-2, F-3 and F-4 were 44%, 30%, 38% and 31% respectively. Through the entire experimental period surfactants showed retarding and uniform release for all the formulations.

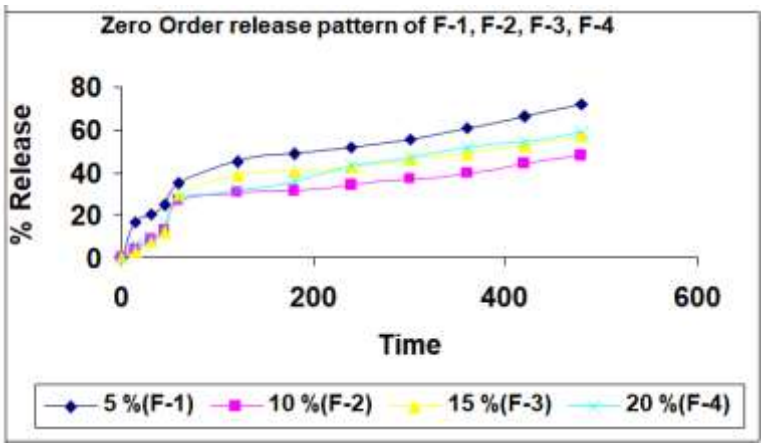



**Figure 1(a): Zero –order plot of release kinetics of naproxen sodium from compressed microcapsules**

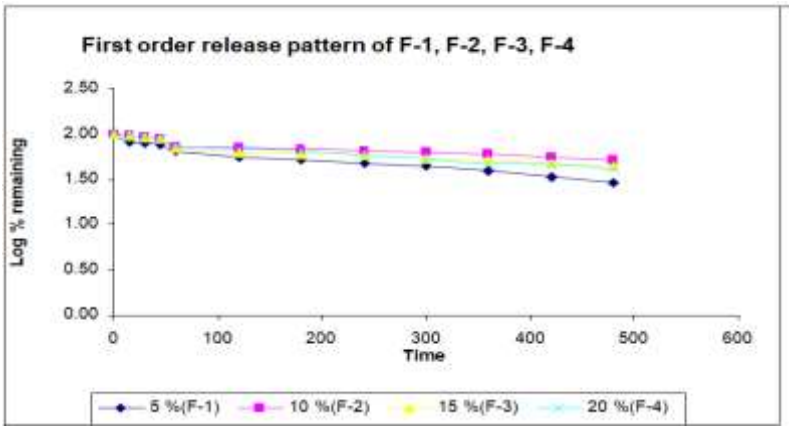



**Figure 1(b): First order plot of release kinetics of naproxen sodium from compressed microcapsules**

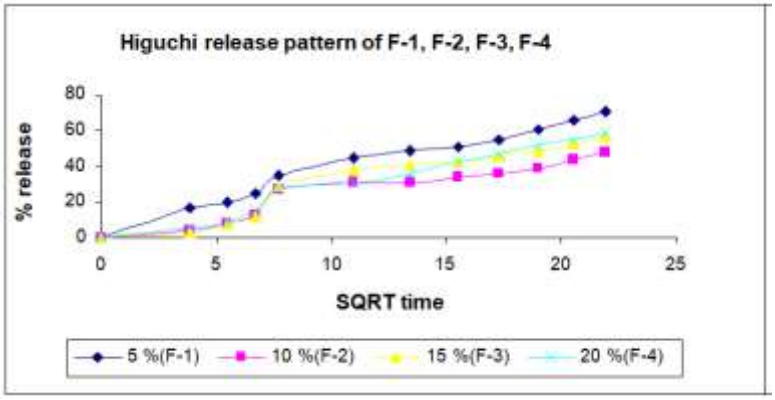



**Figure 1(c): Higuchi plot of release kinetics of naproxen sodium from compressed microcapsules**

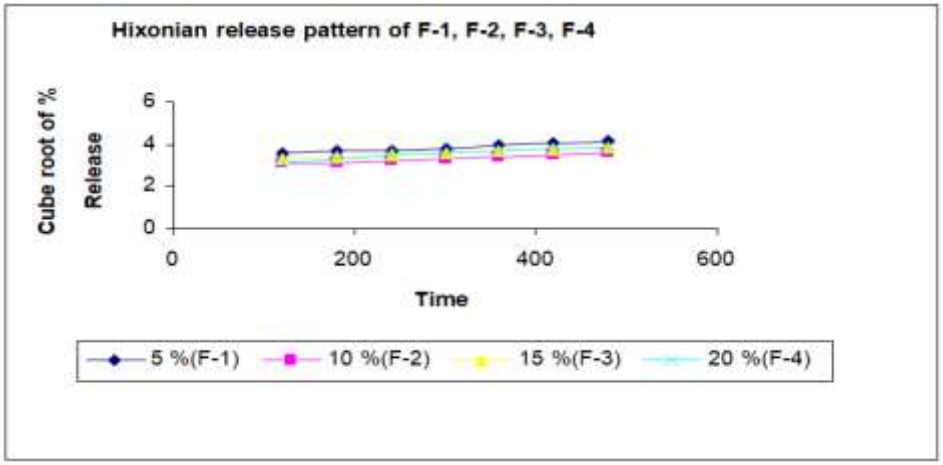



**Figure 1(d): Hixonian plot of release kinetics of naproxen sodium from compressed microcapsules**

The analysis of mechanism of drug release from pharmaceutical device is important but complicated. Therefore several equations were suggested for this purpose. To investigate the effect of talc (5%, 10%, 15% and 20% respectively) on naproxen sodium release, four formulations were prepared (table-1). The formulation and release data were treated in kinetic models like zero order, first order, higuchian and hixon crowell. Hixon crowell was used to calculate the release exponent (n) and mean dissolution time ($T_{50\%}$). The general form of this equation:

$$\sqrt[3]{M_0} - \sqrt[3]{M} = K_c t \qquad (V)$$

Where $K_c$ is the cube root dissolution rate constant, $M_0$ is the initial amount of drug, M is the amount of drug remaining.

### Correlation coefficient and diffusion exponent (n):

In this experiment all the four formulations prepared with talc 5%, 10%, 15% and 20% bets fits with hixon (R2= 0.99) kinetic model to the same extent for all respective batches as showed in table 3. When $3\sqrt{M0}$ and $3\sqrt{M}$ was plotted against t, the values of diffusion exponent, n were find out for microcapsules and matrices of different system with correlation coefficient. Hixon used this n value in order to characterize different release mechanisms. For spherical matrices, if n ≤0.43, a fickian diffusion, 0.43 ≤n<0.85, a non-fickian diffusion transport and n≥0.85, a case-II transport (zero order) drug release mechanism takes place. For polydisperse spherical systems, the value of n as low as 0.3 and 0.45 for fickian diffusion for F-1, F-2 and F-3 are 0.38, 0.42 and 0.33 respectively, and non-fickian diffusion or anomalous transport for F-4, the n value is 0.49. Different mechanism showed for talc concentration variation may be due to the saturation of pores of polymer surface when the concentration is lower. When the concentration of talc is increased the pores become saturated and initially they cause erosion of talc layer on the surface and then leaching of the dissolution media creating pores and then release of the drug through pores.

**Table 3: Correlation co-efficient ($R^2$), release rate (K), release exponent (n) and $T_{50\%}$ MDT value of different formulations of naproxen sodium from kollidon® SR microcapsules using different concentration of talc**

| Formulation | n | MDT | | | Zero order | | First order | | Higuchian order | | Hixonian order |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $T_{25\%}$ | $T_{50\%}$ | $T_{80\%}$ | $R^2$ | K | $R^2$ | K | $R^2$ | K | $R^2$ |
| F-1 | 0.38 | 3.00 | 6.00 | 3.75 | 0.86 | -0.00 | 0.94 | 3.03 | 0.97 | 0.001 | 0.99 |
| F-2 | 0.42 | 7.50 | 15.00 | 24 | 0.83 | -0.05 | 0.82 | 2.18 | 0.93 | 0.001 | 0.97 |
| F-3 | 0.33 | 6.00 | 12.00 | 19.2 | 0.82 | -0.00 | 0.88 | 2.76 | 0.92 | 0.001 | 0.99 |
| F-4 | 0.49 | 4.00 | 8.00 | 12.8 | 0.90 | -0.00 | 0.95 | 2.78 | 0.97 | 0.002 | 0.97 |

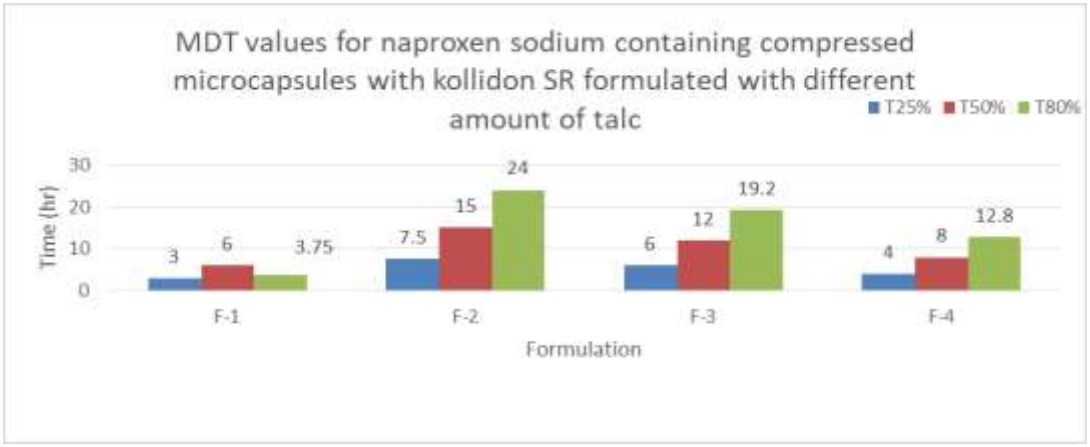



**Figure 2: Different MDT values of naproxen sodium from compressed microcapsules**

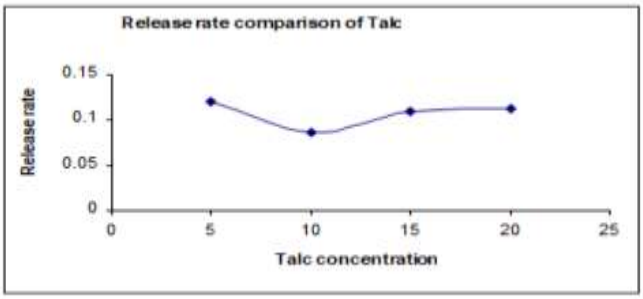
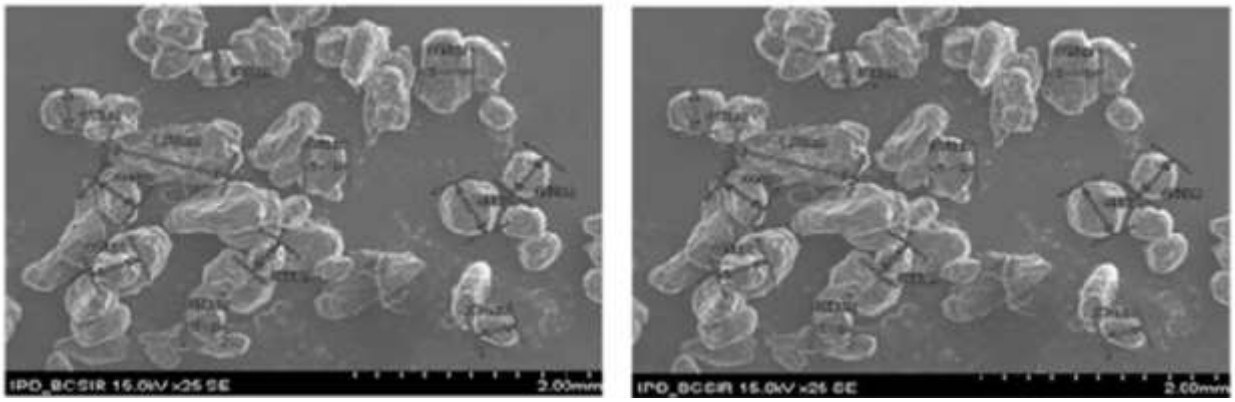



**Figure 3: Release of naproxen sodium from different formulations of kollidon® SR based compressed microcapsules containing varying amount of talc.**

To characterize the drug release rate in different experimental formulations, mean dissolution time (MDT) was calculated. From the table 3, it is clear that T50% (MDT) values were changed due to the change of amount of talc in the microcapsules. The values of T50% (MDT) increases with the higher concentration of talc. This may be due to the settling down of talc particle on the polymer surface thus blocking of pores of microcapsules. A graphical representation of T50% (MDT) values is shown in figure 2. Figure 3 exhibits the release pattern of drug from different concentration of talc.

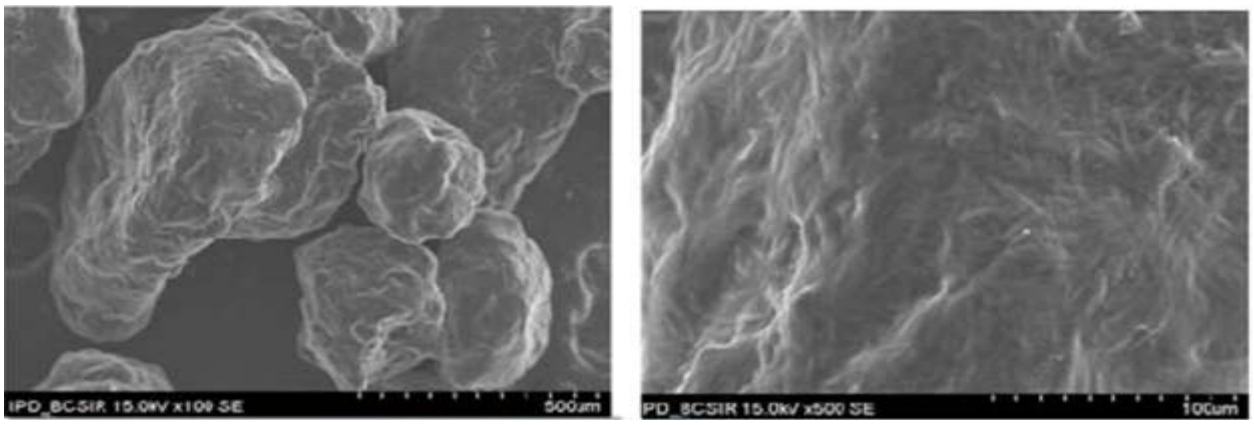
**Scanning electron microscope analysis:**

kollidon® SR microcapsules loaded with naproxen sodium were examined by scanning electron microscope (SEM, S-3400N, Hitachi) to observe the morphological and particle size changes that occurred due to the formulation variation (Figure 4,5 and 6). Morphology and surface properties were found to be affected by the varying talc concentration. Out of the four concentration 10% of talc made the pores most saturated and finally the talc settled down on the surface and produced smooth continuous surface. This yielded best drug release performance with the increase in concentration of talc and higher mean dissolution time ($T_{50\%}$) for drug release as signified in table 3.



A B

**Figure 4: Scanning electron microscopy of F-2 (Magnification-A. 15.0kv x 25 SE, B. 15.0kv x 25 SE scale magnification)**




C D

**Figure 5: Scanning electron microscopy of F-2 (Magnification-C. 15.0kv x 100 SE, D. 15.0kv x 500 SE)**

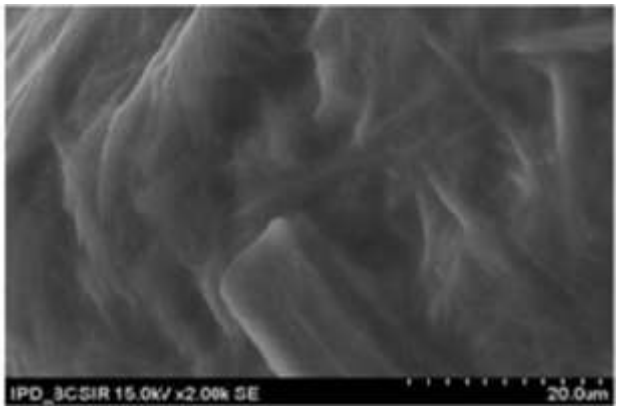



**Figure 6: Scanning electron microscopy of F-2 (Magnification-E. 15.0kv x 2.00K)**

## CONCLUSION:

Highly significant result has been observed for Talc 10%. According to Hixonian kinetics in 15 hours, only 50% of drug has been released in Fickian or diffusion controlled released order. The effect of Talc on the release of Naproxen sodium compressed tablets was shown in Table 3. Matrix tablets containing various Talc concentrations were prepared by emulsification and solvent evaporation technique. The variation of drug release pattern was found with the variation of talc concentration which thereafter directly affected the release kinetics of the drug. The drug release was lowered with the 10% concentration of talc used in the formulations.

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