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Design and *in-vitro* evaluation of compressed Kollidon® SR based Salbutamol Sulphate microcapsules: Effect of talc

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ABSTRACT

Salbutamol sulphate, a bronchodilator drug for asthma, was encapsulated by (W/O) emulsion-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 performed to study the 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 XXX paddle method (type 2) in 400 ml distilled water (pH 7.4) for 8 hours at $37^0 \pm 5^0$ C temperature at 50 rpm. Release of salbutamol sulphate from the compressed microcapsules was found to follow Higuchi mechanism (R^2=0.99). Korsmeyer equation was used to calculate the release exponent value (n) which indicates the drug release behavior and the mean dissolution time $T_{50\%}$ (MDT) for release rate. The surfaces of the microcapsules became smoother with the increase in talc concentration and simultaneously decrease in drug release rate.

Key words: Salbutamol sulphate, kollidon® SR, sustained release, microcapsule, emulsion-solvent-evaporation technique.

INTRODUCTION

Salbutamol sulphate is fairly soluble in water and therefore the construction of a sustained release product in microcapsules is more convenient [1]. Sustained release microcapsule preparations are frequently been prepared by dispersing drug particles in polymer matrices where the polymer is to act as a rate controlling barrier [2]. Many studies on the preparation of biodegradable microcapsules have been reported concerning their morphological and physico-chemical properties [3,4]. Salbutamol is a sympathomimetics amine which is used as a

bronchodilator in the treatment of reversible bronchospasm. It is absorbed rapidly when administered orally. The plasma half-life of salbutamol was calculated to be 2-7 hrs. [5]. Its usual dose is 2-4 mg, 3-4 times daily [6]. In the present 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. This water insoluble polymer (povidone part is water soluble but polyvinyl acetate part is water insoluble) can be used in different types of sustained release dosage forms like tablets, pellets and granules [7]. But its excellent flow ability and compressibility makes it suitable for sustained release matrix tablet by direct compression [7-10]. 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 [11-13]. In this paper the effect of variable concentrations of talc on release of salbutamol sulphate from kollidon® SR based compressed microcapsules have been discussed.

EXPERIMENTAL SECTION

Salbutamol sulphate was collected from (PHARMARAW, India), Kollidon® SR from the regional office of BASF, Germany in Bangladesh, Liquid paraffin oil light (MERCK, Germany), 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 salbutamol sulphate microcapsules

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

Table 1: Formulations, drug loading efficiency and avg. microcapsule size of different batches of microcapsules of salbutamol sulphate with kollidon® SR.

Formulation	Materials					Drug Loading (%)			Avg. size (µm)
	SBS (gm)	KSR (gm)	Talc (gm)	Methanol (ml)	Span60 (gm)	Theoretic	Actual	Loading efficiency	
F-1	4	3.8	0.2	20	1	50	45.99	91.98	215
F-2	4	3.6	0.4	20	1	50	42.10	84.20	213
F-3	4	3.4	0.6	20	1	50	48.62	97.24	-
F-4	4	3.2	0.8	20	1	50	48.52	97.04	337

**SBS= Salbutamol sulphate, *KSR= Kollidon® SR*

At first a kollidon® SR solution was prepared at a drug polymer ratio of 1:1 by dissolving kollidon® SR in methanol which acts as internal phase. Liquid paraffin oil was emulsified using span 60 with the help of stirrer at 3000 rpm. Then talc and salbutamol sulphate was dispersed in the emulsified external phase. A volume of previously prepared polymeric internal phase containing kollidon® SR was slowly added to the external phase and stirred for about 2 hours keeping the same rpm. After 2 hours the prepared microcapsules were washed by petroleum ether (40:60) and were allowed to dry in the natural air for about 2 or 3 days. 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 in table 1.

Assay of microcapsules

A few mg of kollidon® SR microcapsules containing salbutamol sulphate was taken in a mortar and was triturated properly until fine powder was formed. 30 mg of fine powder of microcapsules were taken in a 100 ml volumetric flask with the help of a funnel. Few ml of distilled water (pH 7.4) was added with the powdered microcapsules, 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 276 nm. Using the absorbance value, the amount of salbutamol sulphate entrapped was determined with the help of standard curve.

The loading efficiency was assumed 50% for each batch. The data loading efficiency of each batch is represented in table 1.

Loading efficiency was calculated by using the following equation:

$$\text{Loading efficiency} = \frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \times 100$$

Preparation of compressed microcapsules

Compressed microcapsules were prepared according to table 2 by using the direct compression method. HPMC 50 cps was used as a polymer for all the formulations. The appropriate amount of microcapsules were calculated and weighed that contained equal amount of drug. Then HPMC 50 cps were weighed and mixed properly with the measured microcapsules. After that the mixture was compressed on a single punch tablet machine (Perkin-Elmer laboratory hydrophilic press equipped with 13 mm faced punch and die set). The compression force and compression time were 5 ton and 30 seconds, respectively. The final weight of compressed microcapsules were made to 300 mg each.

Table: 2. Formulation of compressed microcapsules of salbutamol sulphate with kollidon® SR

Formulations	Amount of MC (mg)	HPMC (mg)	Total weight (mg)
F-1	87	213	300
F-2	95	205	300
F-3	79	221	300
F-4	82	218	300

MC= Microcapsule

***In-vitro* dissolution study**

In-vitro dissolution study was performed in a paddle type dissolution apparatus (USP Type III Dissolution Apparatus, VEEGO, INDIA). 400 ml of Distilled water (pH 7.4) was used as dissolution media, paddle speed was set at 50 rpm, and temperature was maintained at 37ºC. The compressed microcapsule of each batch was transferred in each dissolution basket. The dissolution process was carried out for 8 hours and 10 ml of dissolution sample from each batch was withdrawn at a predetermined time intervals (15, 30, 45, 60, 120, 180, 240, 300, 360, 420 and 480 minutes). Each and every time 10 ml dissolution sample was compensated by fresh 10 ml distilled water. Dissolution samples were withdrawn with the help of 12 ml syringe and were

taken 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 wave length of 276 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 models.

- The zero order equation assumes that drug release is constant:
  $M=M_o-K_ot$ …… (I)

In this equation M is the amount of drug remaining undissolved at time t, M_o is the amount of drug undissolved at t=0 and K_o is the corresponding release rate constant.

- A form of the Higuchi Square Root Law is given by equation:
  $Q=K_s \sqrt{t}$ ……. (II)

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

- Release behavior generally follows the following first order release equation:
  $\ln M=\ln M_oK_1t$ ……. (III)

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

- The Korsmeyer's equation which derived from the linear line of log cumulative percentage versus log time curve is:
  $M_t/M_\alpha = K_kt$ …….. (IV)

Where K_k is the Korsmeyer release rate constant.

Particle size, size distribution and surface morphology study

Surface nature, size and size distribution of the microspheres were examined with the help of Scanning Electron Microscope (S-3400N, Hitachi, Japan). 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 and 15.0 kv X 2.00k SE. The average particle size was determined by measuring the Martin's diameter [14].

RESULTS AND DISCUSSION

Effect of talc on the release pattern of salbutamol sulphate from kollidon® SR based compressed microcapsules

Four different concentrations of talc were used which possess 5%, 10%, 15% and 20% of talc for F-1, F-2, F-3 and F-4 respectively. The drug loading efficiency of was assumed 50% for each batch. 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 salbutamol sulphate from compressed microcapsules with kollidon® SR with varying talc concentrations to the polymer. In this study the percent drug release was decreased with increase of talc concentration although insignificant variation in their release throughout the dissolution tests period was noted. The initial burst release was nearly similar for F-1, F-2 and F-3 about 53.25%, 55.31% and 51.89% respectively while it was 43.12% for F-4. The burst release was observed after 2 hours. After the end of 8 hours of dissolution study, the approximate percent release of salbutamol sulphate for F-1, F-2, F-3 and F-4 were 98%, 97%, 90% and 86% respectively. Through the entire experimental period surfactants showed a retarding as well as uniform release for all batches.

Zero-order release of salbutamol sulphate from Kollidon® SR based compressed microcapsules

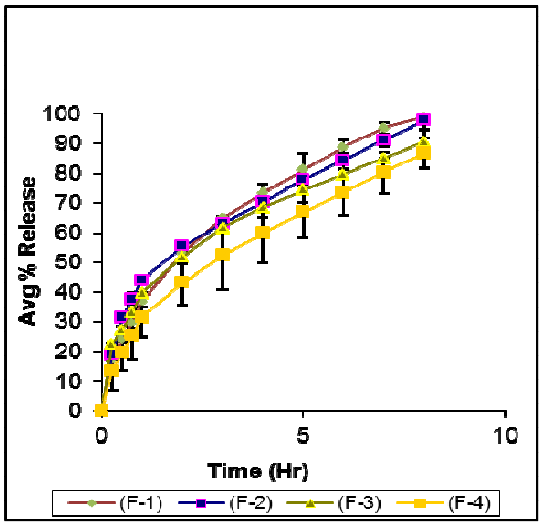


Figure 1(a) Zero-order plot of release kinetics of salbutamol sulphate from compressed microcapsules.

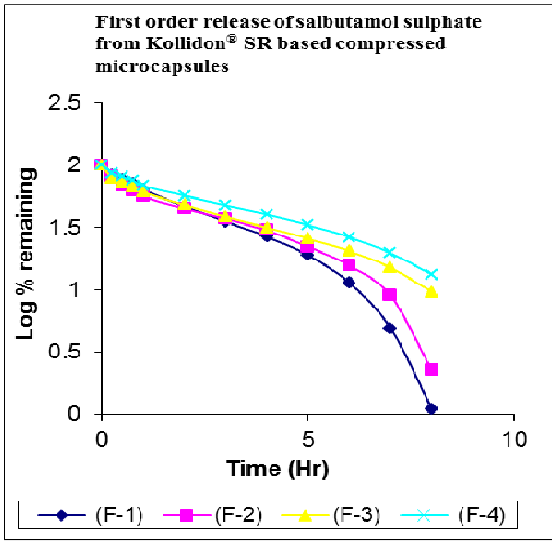


Figure 1(b) First-order plot of release kinetics of salbutamol sulphate from compressed microcapsules

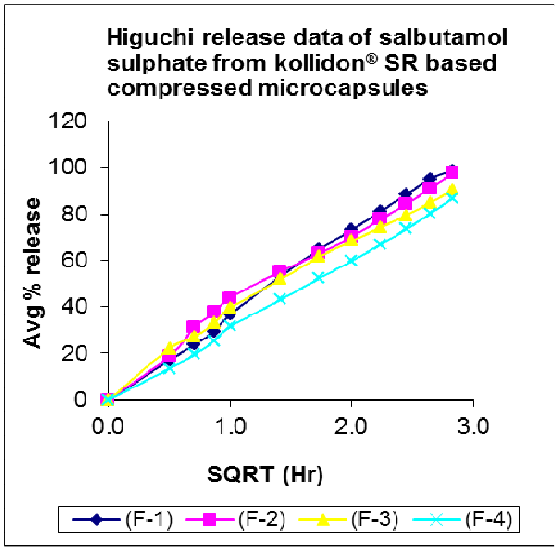


Figure 1(d) Korsmeyer plot of release kinetics of salbutamol sulphate from compressed microcapsules.

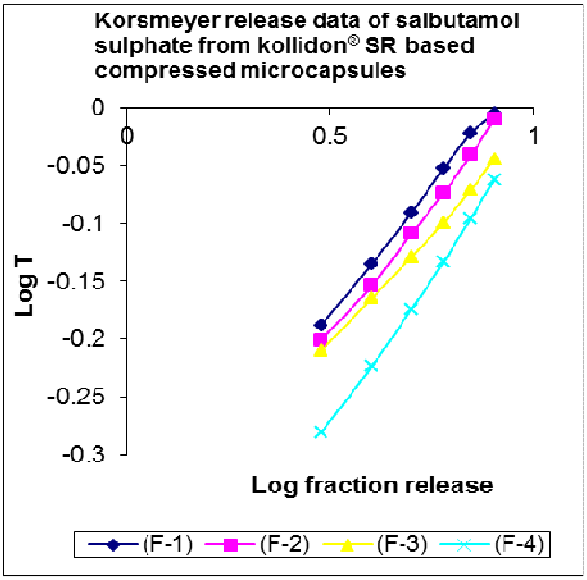


Figure 1(c) Higuchi plot of release kinetics of salbutamol sulphate from compressed microcapsules.

The analysis of mechanism of drug release from pharmaceutical device is important but complicated. Therefore several equations have suggested for this purpose [15].

To investigate the effect of talc (5%, 10%, 15% and 20%, respectively) on salbutamol sulphate release, four formulations were prepared (table-1). The formulation and the release data were treated in kinetic models like zero order, first order, and Higuchi. Korsmeyer equation was used to calculate the release exponent (*n*) and mean dissolution time $T_{50\%}$ (MDT). Korsmeyer *et.al* and Peppas presented a simple semiemperical equation which can be used to analyze data of controlled release of water soluble drugs from the polymers [15,16]. The general form of this equation is:

$$M_t/M_\infty = K_t^n \ldots\ldots\ldots\ldots \text{(vi)}$$

Where, M_t/M_∞ is the fractional release, K is the kinetic constant and n is the diffusion exponent, characteristic of the mechanism of diffusion release.

Correlation coefficient and diffusion exponent (n)

In this experiment all the four formulations prepared with talc 5%, 10%, 15% and 20% best fits with Higuchi (R^2 = 0.99) kinetic model to the same extent for all respective batches as showed in table 3.

When M_t/M_∞ was plotted against log t, the values of diffusion exponent, n were found out for microcapsules [17] and matrices of different system with correlation coefficient**.** Peppas use this *n* value in order to characterize different release mechanisms. For spherical matrices, if $n \leq 0.43$, a fickian diffusion, $0.43 \leq n < 0.85$, a non-fickian diffusion transport and $n \geq 0.85$, a case-II transport (Zero order) drug release mechanism dominates. In case of polydisperse spherical systems, the value of *n* as low as 0.3 and 0.45 for fickian and case-II transport, respectively [18]. The values from the table 3 supports fickian diffusion for F-3 *n*(0.39) and non-fickian diffusion or anomalous transport for rest of the F-1, F-2 and F-4 formulations *n* (0.44, 0.45 and 0.51) respectively. Different mechanism showed for tale concentration variation may be due to the saturation of pores of polymer surface when the concentration is lower. When the concentration of talc increased the pores become saturated and initially they cause erosion of tale layer on the surface and then leaching of the dissolution media creating pores and then release of the drug through them.

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

Formulation	Zero order		First order		Higuchi		*n*	MDT		
	R^2	K	R^2	K	R^2	K		$T_{25\%}$	$T_{50\%}$	$T_{80\%}$
F-1	0.93	11.39	0.91	-0.20	0.99	36.07	0.44	1.23	2.45	3.92
F-2	0.89	10.15	0.90	-0.16	0.99	32.07	0.45	1.34	2.68	4.29
F-3	0.89	9.51	0.99	-0.11	0.99	30.71	0.39	1.43	2.85	4.56
F-4	0.94	9.70	0.98	-0.09	0.99	30.62	0.51	1.83	3.65	5.84

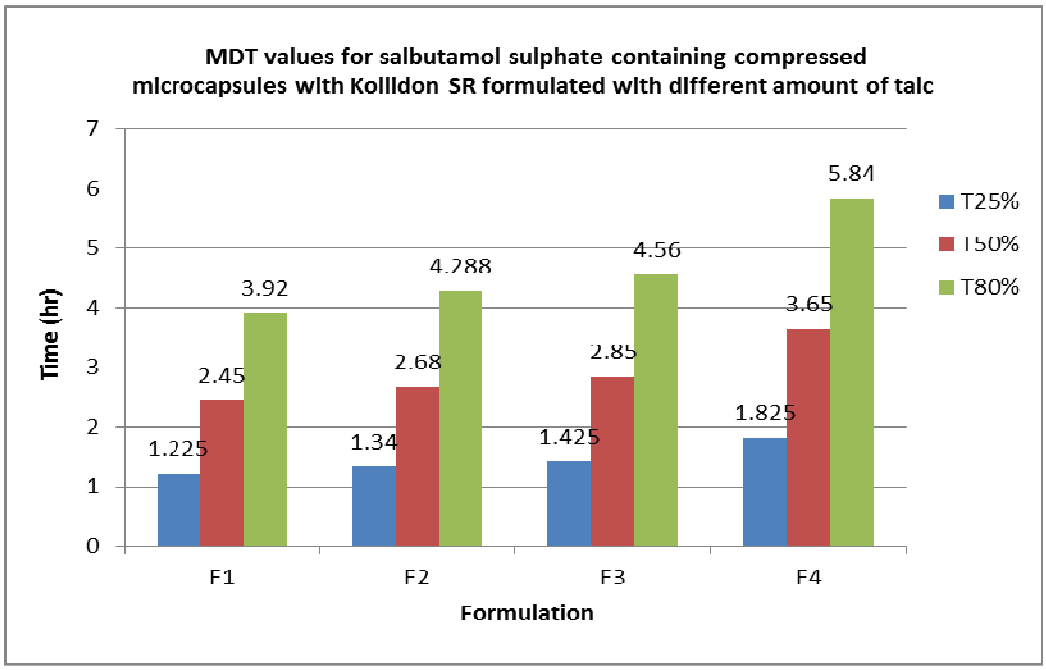


Figure 2. Different MDT values of salbutamol sulphate from compressed microcapsules.

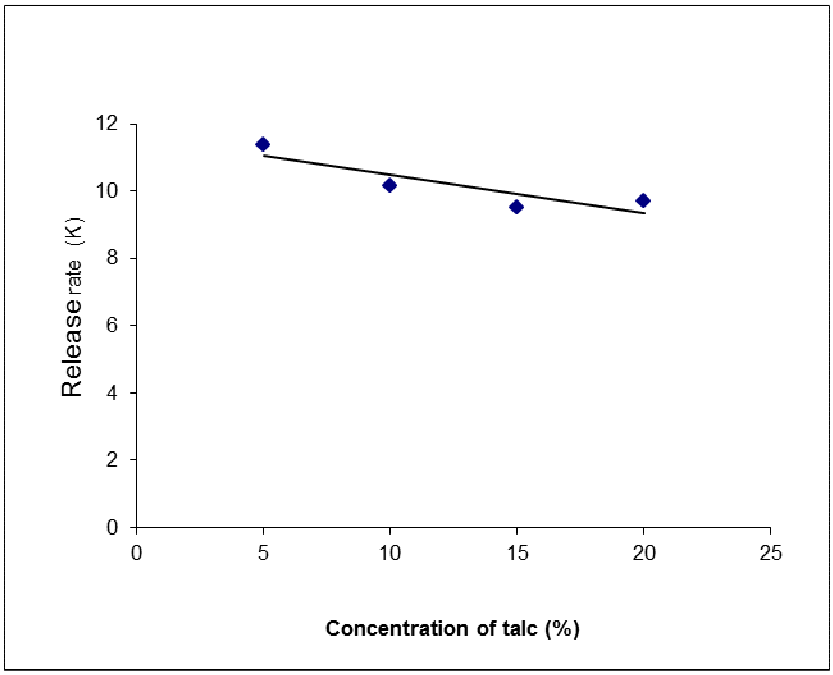
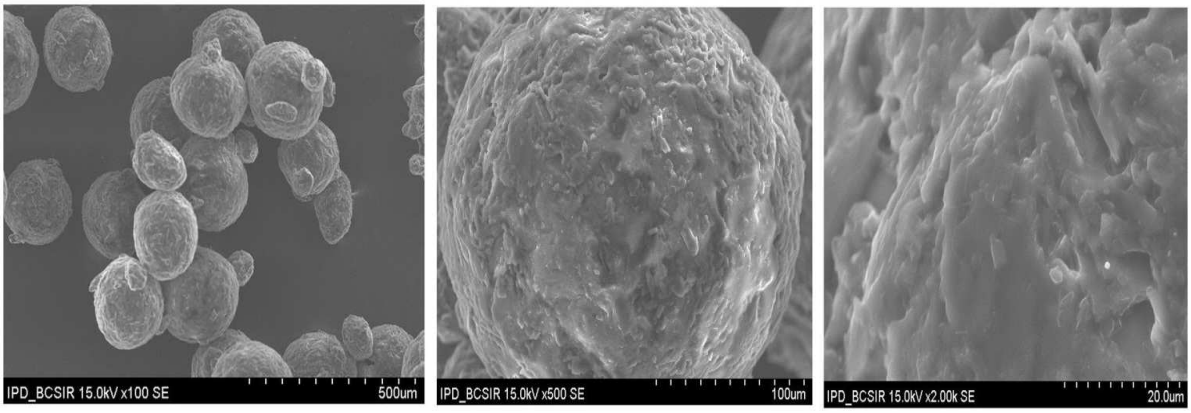


Figure 3. Release rate of salbutamol sulphate from different formulations of kollidon® SR based compressed microcapsules containing varying amount of talc.

To characterize the drug release rate in different experimental formulations, mean dissolution time (MDT) was calculated. From the table 3, it is clear that $T_{50\%}$ (MDT) values were changed due to the change of amount of talc in the microcapsules. The values of $T_{50\%}$ (MDT) increases with the higher concentration of talc. This is may be due the settling down of talc particle on the polymer surface thus blocking of pores of microcapsules. A graphical representation of $T_{50\%}$ (MDT) values is shown in figure 2 and the release rate also determined from zero-order curve as shown in figure 3 which exhibited a linear relationship.

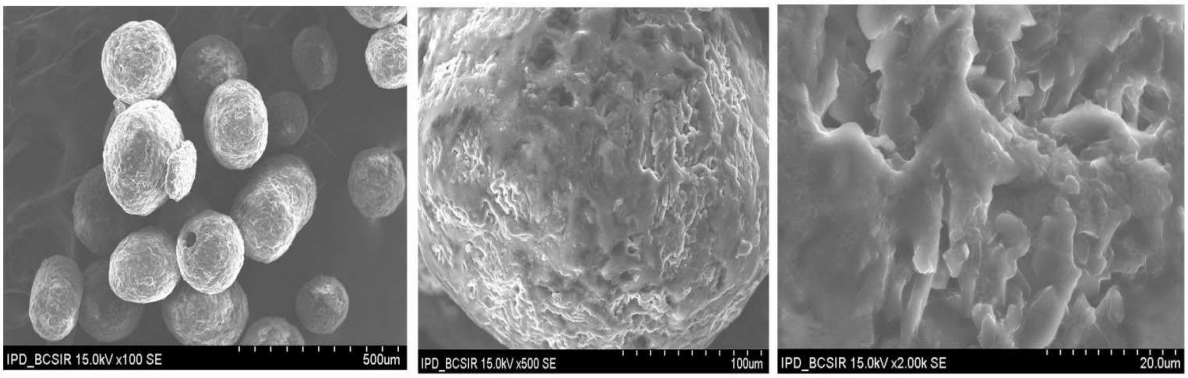
Scanning electron microscopic analysis

Kollidon® SR microcapsules loaded with salbutamol sulphate were examined by scanning electron microscope (SEM, S-3400N, Hitachi) to observe the morphological changes and the 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. The average particle size was determined which is revealed in the table 1. As the concentration of talc was increased the surface became smoother. Initially the crystalline talc blocked the pores on the kollidon® SR polymer surface and when 10% talc was used the pores became more saturated and finally the talc settled down on the surface and produced smooth continuous surface offer using 20% talc. This finding might be beyond the 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.



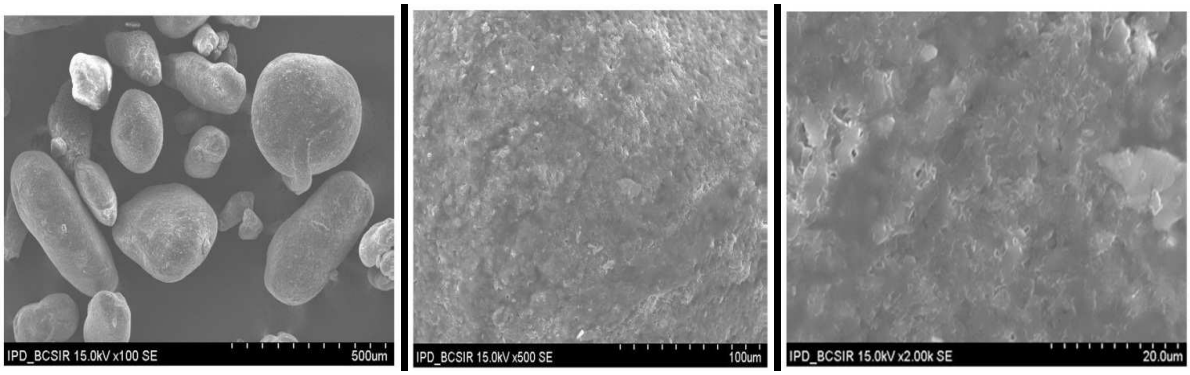
A **B** **C**

Figure 4: Scanning electron microscopic picture of F-1 (Magnification- A. 15.0kV×100 SE, B. 15.0kV×500 SE and C. 15.0kV×2.00k SE)



A **B** **C**

Figure 5: Scanning electron microscopic picture of F-2 (Magnification- A. 15.0kV×100 SE, B. 15.0kV×500 SE and C. 15.0kV×2.00k SE)



A **B** **C**

Figure 6: Scanning electron microscopic picture of F-4 (Magnification- A. 15.0kV×100 SE, B. 15.0kV×500 SE and C. 15.0kV×2.00k SE)

CONCLUSION

The microcapsules of kollidon® SR with salbutamol sulphate were prepared successfully by (W/O) emulsion solvent evaporation technique using four different concentration of talc although very few efforts have been reported on the application of widely used matrix polymer kollidon® SR for microcapsule preparation. 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 higher concentration of talc used in the formulations. The change in drug release pattern from microcapsules with kollidon® SR should be examined with other variables for more the establishment of this as useful polymer for microencapsulation.

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REFERENCES

[1] Khalil, S.A.H. and Elgamal, S.S. *J. Pharm. Pharma-col.* **1971**; 23: 72-74.
[2] Goto, S. *Proceeding of the 9th international symposium on micro encapsulation, Ankara, Turkey, Sept.* **1993**; 84.
[3] Jalil, R. and Nixon, J.R. *Journal of microencapsulation*, **1990**; 7: 25-39.
[4] Iwata, M. and Mcginity, J.W. *Pharmaceutical research*, **1993**; 10: 1219-1227.
[5] James E. F. Reynolds and Anne B. Prasad. Martindale: The extra pharmacopeia, 28th Edition, The Pharmaceopeial Press, London, **1982**; 29-33.
[6] Yazan, Y. Demirel, M. and Güler, E. *J Microencapsulation*, 1994; 12: 601-607.
[7] BASF, Technical information, April 2006.
[8] Hauschild, K. and Picker-freyer, K.M. *Pharm Dev Technol*, **2006**; 11:125-40.
[9] Khanz, H., Le Brun,V. and Wagner, T. T. *Int. J. Pharm.*, **2005**; 11, 299, 84-91.
[10] Shao, Z. j., Farooqi, M. I. Diaz, S., Krishna, A.K. and Muhammad N. A. *Pharm. Dev. Technol.*, **2001**; 6: 247-254.
[11] Zinutti C, Kedzierewicz F, Hoffman M, Maincent P. *J Microcapsulation*, **1994**; 11: 555-563.

[12] Zinutti, C., Kedzierewicz, F., Hoffman, M., Benoit J.P., Maincent P. *Int J Pharm,* **1996**; 133: 97-105.
[13] Owusu-Ababio G, Rores, J.A. and H. Anwar. *Int. J. Pharm.* **1995**; 122: 9-15.
[14] Martin, A. 1993. Colloids. In: Physical Pharmacy: Physical and Chemical Properties in Pharmaceutical Sciences (Martin, A. Ed.) 4th ed., Lea and Febiger, Philadelphia, P. A., pp. 393-422, 453-476.
[15] Korsmeyer, R.W., Gurny. R., Doelker, E. Buri, P. and Peppas, N.A. *Int. J. Pharm.* **1983**; 15: 25-35.
[16] Peppas, N.A. *Pharm. Acta Helv.* **1985**; 60: 110-111.
[17] Sinclair, G.W., and Peppas, N.A. *J. Membrane. Sci*. **1984;** 17: 329-331.
[18] Lee S., Kim M.S., Kim S., Park J.H., Woo J. S., Lee B.C. and Hwang S.J. *J. Microcapsule* **2006;** 23(7): 741-749.