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# Evaluation of Tableting Properties of Agglomerates Obtained by Spherical Crystallisation of Trimethoprim

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**Trimethoprim (TMP) crystals exhibit poor flow properties, compressibility as well as slower dissolution rates. Spherical agglomerates (SA) of TMP were prepared by simple spherical crystallisation process. The crystallisation system consisted of water-methanol-chroform with PEG (SA-I) and PEG-PVP (SA-II). Agglomerates were characterised using TLC, XRD, IR and evaluated for micromeritic, mechanical, compressional, wetting and dissolution behaviour. SA-II has shown reduction in crystallinity and high 'a' and low 'b' values of Kawakita constants. Change in friability index was lowest for SA-I. But SA-I and SA-II both have very low crushing strength. TMP showed poor compressibility. SA-I exhibited lower $P_y$ value and contact angle compared with SA-II. Cumulative release was higher from SA-II but $D_{5\ min}$ for SA-I is significantly higher than SA-II.**

POWDERS can rarely be compressed directly into tablets and generally requires pretreatment to ensure tablet formation. The pretreatment involves modification and design of pharmaceutical powder drugs so as to improve the properties, such as flowability, packability, solubility and bioavailability of the product. Recently spherical crystallization, a novel multiple operation process, has been adopted to improve compressibility of poorly compressible drugs[1].

TMP was used as the model drug because of its characteristic monoclinic and triclinic crystals having very poor flow properties, compressibility as well as slower dissolution rates. The spherical agglomerates of TMP were prepared by simple spherical crystallization method[2].

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## MATERIAL AND METHODS

### MATERIALS

Trimethoprim (Gift sample supplied by Piramal Healthcare Ltd. Bombay), PEG 6000 (Burdidges and Co. Ltd. Bombay), and PVP K-30 (Research Lab. Bombay).

### Preparation of spherical agglomerates:

Spherical crystallisation was carried out in a vessel designed by Morishima *et al*[1], TMP (4 g) was dissolved in a mixture of methanol (40 ml) and chloroform (10 ml) controlled at temperature of 50°. The solution was poured into 400 ml PEG (1 % w/v) aqueous solution. The system was agitated at 1000 rpm. and the resulting spherical agglomerates (SA-I) were filtered and dried. The same procedure was followed using aqueous solution containing PEG and PVP (0.5% w/v each) and agglomerates (SA-II) were obtained.

### Characterization of agglomerates:

TMP and spherical agglomerates were characterised using Thin Layer Chromatography ($CHCl_3$ : $CH_3OH$, 1:9).

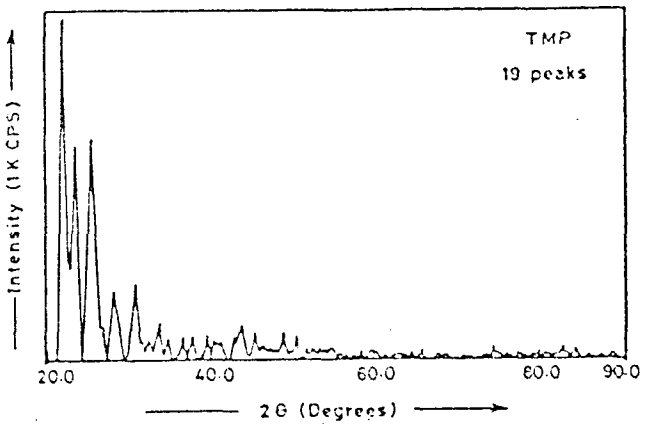


**Fig. 1a: X-ray Diffractogram ofTMP**

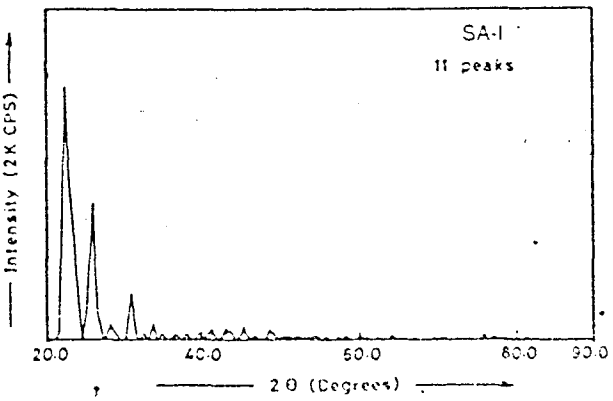


**Fig. 1b: X-ray Diffractogram of SA-I**

Powder X-Ray Diffraction (X-ray diffractometer, Rigaku, Japan), Infra-Red Spectrum (FTIR spectrometer, Perkin Elmer, U.S.A.) using Nujol and thermogravimetric analysis was carried out by thermogravimetry (Perkin Elmer, U.S.A.)

**Evaluation of agglomerates:**

**1) Micromeritic Properties** : Flowability of TMP and spherical agglomerates was assessed by determination of angle of repose by fixed funnel method[3]. Packability of Shperical agglomerates was determined by Kawakita Equation[4].

$$n/C = 1/(ab) + n/a \quad C = Vo-Vn/Vo \quad \text{.....(i)}$$

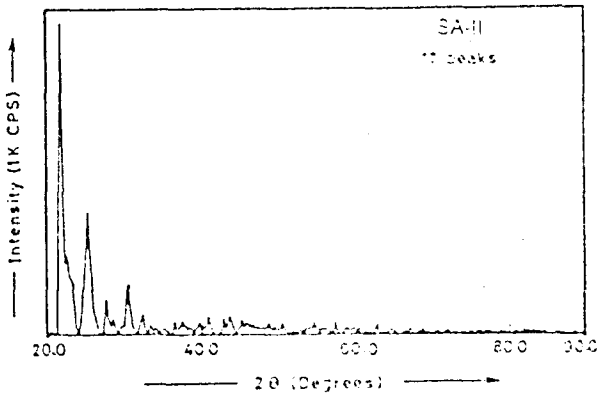


**Fig. 1c: X-ray Diffractogram of SA-II**

where 'n' is number of tappings, 'C' is ratio of difference in the initial volume and final volume after nth tapping to the initial volume and final volume, and 'a' and 'b' are constants that represent flowability and packability.

**2) Mechanical properties** : Spherical agglomerates were evaluated for crushing strength and friability. Crushing strength was determined by Jarosz and Parrott load cell method[5]. Friability was studied by modification on Lin and Peck method, in which sample (10 g) with size of # 14/85 and 20 plastic balls (each of 0.95 cm Dia. and 530±10 mg weight) were placed on #85 and shaken using Ro-Tap sieve shaker for 5 min. The fraction passing through 85 mesh at the end of 5, 10, 15, 20 and 30 minutes treated using a linear equation:

$$\text{Fines (\%)} = kt + C \quad \text{..... (ii)}$$

where, 't' is the time in min and 'K' and 'C' are constants reflecting overall and surface strength of the material.

**3) Compressibility and dissolution studies:** TMP and agglomerates (500±5 mg) were compressed at compaction pressure of 1, 2, 3, 4 and 7 tons for ten sec. using hydraulic press (Spectralab, India). The results were treated by Heckel equation[7].

$$\ln(1/1-D) = KP + A \quad \text{..... (iii)}$$

**Table 1: Micromeritic and Mechanical Properties**

| Sample | Angle of Repose (o) | Kawakita Constants a | b | Fribility testing K | C |
|---|---|---|---|---|---|
| TMP | 34.00±1.00 | - | | - | |
| SA-I | 16.68±0.949 | 0.124 | 8.57 | 0.627 | 0.31 |
| SA-II | 15.64±0.354 | 0.126 | 7.42 | 1.106 | 4.64 |

**Table 2: Compressional and Dissolution Studies**

| Sample | Compressibility $P_y$ | Rate of T.S. rise | Contact Angle(o) | Dissolution rate $D_{5min}$ | $D_{120min}$ |
|---|---|---|---|---|---|
| SA-I | 0.448±0.07 | 1588±0.15 | 44.33±3.01 | 75.269±0.90 | 98.215±0.68 |
| SA-II | 0.595±0.15 | 1.304±0.16 | 51.33±5.53 | 66.530±0.91 | 98.030±0.34 |

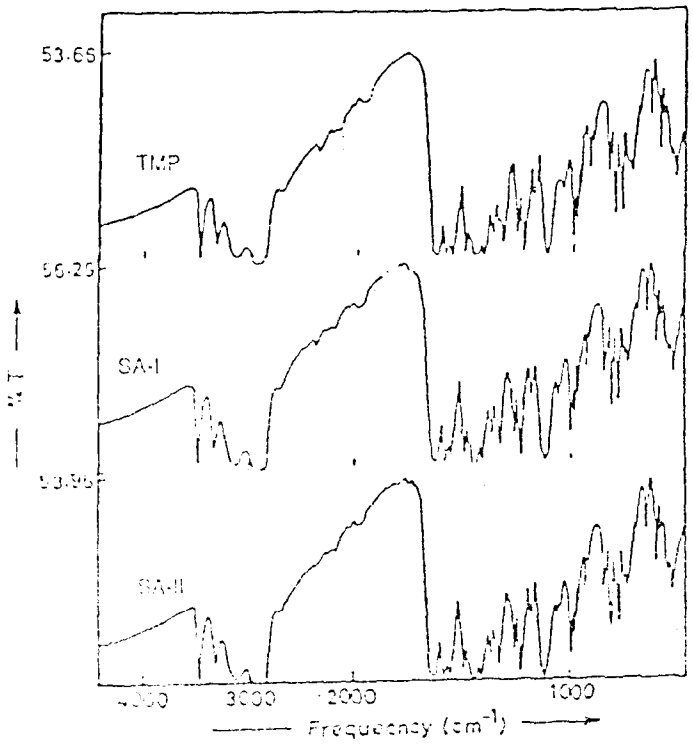


Fig. 2 : I.R. Spectra of TMP, SA-I, SA-II

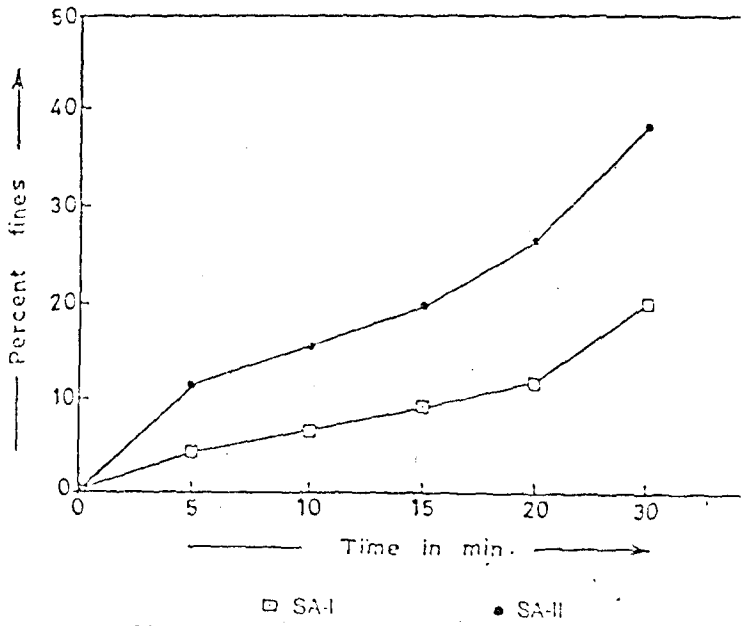


Fig. 3: Friability of Spherical Agglomerates

where, 'P' is compaction pressure, 'D' is packing fraction and 'K' and 'A' are constants.

Tensile strength (T) was calculated by

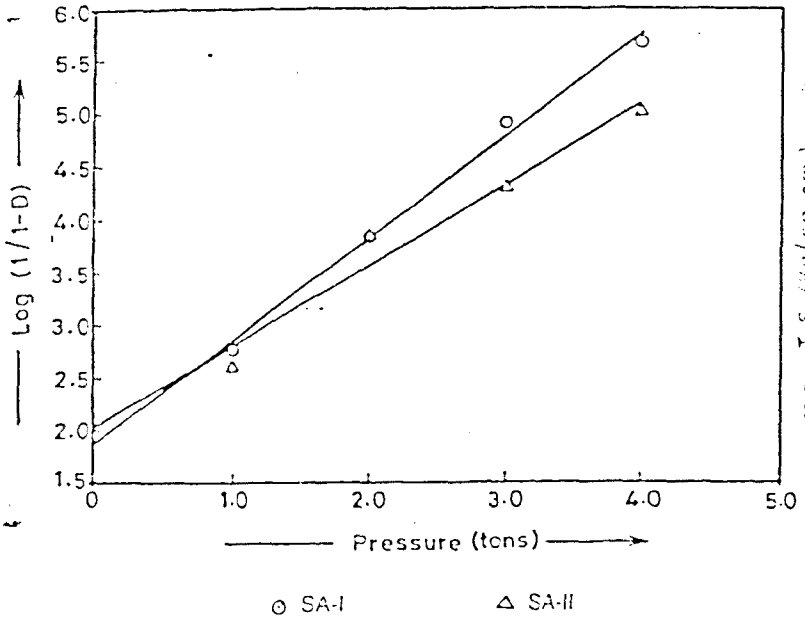


Fig. 4: Heckel Plot of Spherical Agglomerates

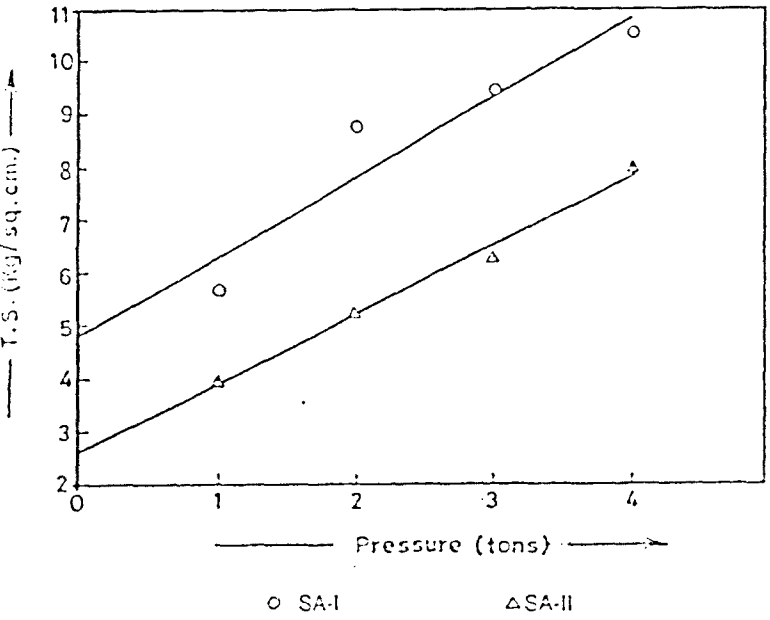


Fig. 5: Effect of Pressure on Tensile Strength of Spherical Agglomerates

$$T = 2P/\pi Dt \quad \text{..... (iv)}$$

where, 'P' is breaking force in Kg, 'D' and 't' are diameter and thickness of compacts in cm. respectively.

In determination of contact angle, 50µl of water was placed on compacts (500±5 mg) prepared at 1 ton for 10 sec. The drop was photographed after 10 sec.

Dissolution rate of compacts (200±2 mg) made at 0.5 tons was carried out in 900 ml of 0.1 N HCL at 37 ± 1° using USP XXI DR-3 dissolution test apparatus (Campbell Electronics Bombay). The absorbance of aliquots was measured at 271 nm using UV-VIS spectrophotometer (Shimadzu 160).

## RESULTS

TLC studies have shown single spot of approximately same intensity with $R_f$ value 0.75, for TMP as well as spherial agglomerates, indicating no complexation between TMP and PEG or PVP. XRD (Fig. - 1) showed 19 peaks for TMP, 17 peaks for SA-II and in case of SA- I number of peaks has decreased to 11 but intensity increased significantly. The reduction in crystallinity in case of SA-II might be attributed to nucleation inhibiting effect of PVP.IR spectras (Fig. -2) show no significant difference in pattern of TMP and agglomerates.

Thermogravimetric analysis of TMP has exhibited single weight loss peak at 278.63°. Similar weight loss peaks were exhibited by SA-I and SA-II at 280° and 268° respectively. But SA-I and SA-II have shown additional peak at 410° and 404° respectively which may be attributed to PEG incorporated in it.

Good flowability and packability of spherical agglomerates was reflected by values of angle of repose and by high 'a' and low 'b' values of Kawakita constants respectively. These results might be attributed to the presence of PEG on the surface of spherical agglomerates, which gives smoothness to the surface. Flowability of SA-II containing PVP cannot be explained in present condition because physicochemical characterization of SA-II has revealed that no significant quantity of PVP is present in the agglomerates. Although PVP is not entrapped during agglomeration process, it might have acted as nucleation inhibitor during crystallisation.

Spherical agglomerates showed poor resistance to crushing but lower friability. Lower values of 'C' and 'K' indicates that change in friability index was lowest for SA-I. As shown in fig.-3, SA-I also showed uniform strength whereas SA-II showed lower surface strength.

SA-I has shown lower $P_y$ values as compared to SA-II (Fig.-4), TMP did not form a compact. The improved

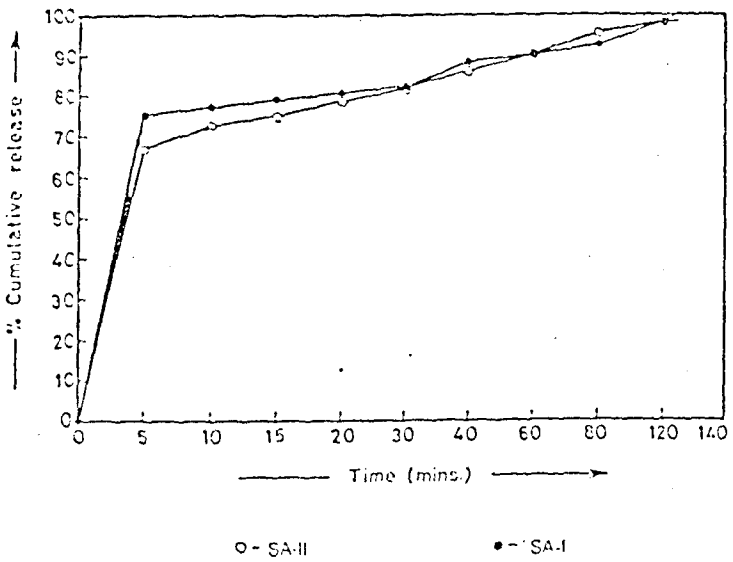


**Fig. 6: Dissolution Profile of Compacts in 0.1N HCl**

compressibility of agglomerates may be attributed to plastic deformation and asperity melting of PEG at points of contact of particles. Tensile strength of compacts increased with increase in compression pressure (Fig.-5). The lower values and slower rise in the tensile strength with pressure for SA-II than SA-I can be explained on the basis of PEG concentration.

Cumulative release (Fig.-6) was higher from agglomerates but $D_{5min}$ for SA-I is significantly higher than SA-II, which is supported by contact angle measurement. High quantity of PEG may be responsible for these results.

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