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Incorporation of METHOCEL E6 PLV by a Novel Foam Granulation Technique for Dissolution Augmentation of the Poor Soluble Silymarin

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ABSTRACT

***Objective*:** In the present study *Foam Granulation Technique* (FGT)™ was employed in the development of IR tablets of high dose of silymarin dried plant extract which is a very fine, poorly compressible material with poor water solubility and these characteristic features poses extensive technological challenge in its manufacturing. ***Methods*:** In FGT, the Methocel E6 PLV was used as foam binder in varying concentrations of 1%, 5%, 7% and 10%. The evaluation of potentially important foam properties, foam penetration mechanism assessment and tablet evaluation was carried out in details and compared with direct compression tablet of silymarin. ***Results and Discussion*:** The foam penetration followed *foam drainage controlled mechanism* and was found to be less dependent on the powder hydrophobicity compared to water drop which followed *drop controlled mechanism.* The foam induced nucleation successfully created nuclei with relatively uniform structure, size and sphericity as compared to water. The dissolution profile of silymarin foam bonded tablets with 5% Methocel E6 exhibited better dissolution profiles with $T_{20\%}$, $T_{50\%}$, $T_{75\%}$ at 6, 30 and 120 min, when compared with direct compression control tablets with $T_{20\%}$ at 120 min. The drug release from optimized 5% foam tablets followed Higuchi model with $R^2 = 0.8831$ and were found to be stable in accelerated stability studies for a period of 3 months. ***Conclusion*:** Thus silymarin with high dose-low solubility characteristics can be easily formulated into IR tablet for clinical and commercial use using this helpful technique.

KEYWORDS: Silymarin, Dissolution, Methocel E6 PLV, Foam binder, Granulation, Solubility.

1. INTRODUCTION

Drug delivery technologies are expanding exponentially with applications in every imaginable route of administration because of the indisputable therapeutic benefits the technology brings but till today tablets as a dosage form rule the pharma world because of the vast array of advantages associated with them (Pai et al. 2011; Banker and Anderson 1987) But the development of high dose tablet of dried plant extract (DPE) as an active ingredient is a complex and extensive technological challenge, as DPEs are quite often very fine, poorly compressible, very hygroscopic and sometimes hydrophobic also (Soares et al. 2005). Several alternative approaches have been proposed to minimize such problems viz dry granulation, wet granulation using non-aqueous solvents, direct compression of DPE, use of different excipients to improve the extract's properties for direct compression etc. (Palma et al. 2002). In tablet manufacturing, wet granulation is used to improve the flow properties and compressibility of granules, but DPEs cannot be granulated using aqueous binder systems due to hydrophobicity issues (Soares et al. 2005; Palma et al. 2002). But in 2003, The Dow Chemical Company (Midland, MI, USA) introduced Foam Granulation Technique™ for delivering aqueous binder systems as foams in high-shear and fluid-bed wet granulation applications demonstrated in a series of case studies and meaningful experiments by Keary and Sheskey, 2004; Sheskey et al. 2004; Sheskey et al. 2006 (Table 1). From then this technology have proved to scale very easily on laboratory and manufacturing scale for both immediate release and matrix controlled-release products; it covers all drugs of different characteristics like High-dose, low-solubility drug; High-dose, high-solubility drug; Low-dose, low-solubility drug and High-dose, high-solubility drug (www.methocel.com) ; it seemed to provide a better and a wider endpoint to granulate even some very difficult actives that we work with, including natural ingredients in the nutritional supplement industry (Sheskey 2008). From the literature it was also noted that the effect of Methocel E6 PLV was found to be more significant with tablets containing low water solubility drugs and higher concentration of drugs within the same solubility classification (Do et al. 2008). Thus the objective of our study was to employ the patented Foam Granulation Technology™ (FGT) in the laboratory

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scale development of silymarin immediate release tablets intended for clinical and commercial use with the help of "METHOCEL" E6 PLV in various concentrations. All the potentially important foam properties, their effects on granule strength, tablet physical-mechanical properties and *in vitro* drug dissolution profiles were extensively studied. No such works have been reported so far on any herbal moiety and this contributed to newness in our studies as silymarin possesses High-dose, Low solubility characteristics - one of class ideal candidate for this type of technique.

Table 1. Comparison between the wet and foam granulation techniques

Wet Granulation	Foam Granulation
Traditionally, an aqueous solution of a binder is sprayed on the powder during mixing in a granulator (Banker and Anderson 1987).	The FGT is a new binder delivery method, where the liquid binder is delivered as aqueous foam to the powder bed (Keary and Sheskey, 2004)
Granulation may appear to be uniform when spraying, but it doesn't always happen.	Uniform distribution of the foam binder evenly throughout a moving powder bed. This can be attributed to the greater surface area of the foam compared with a liquid (Sheskey et al. 2004).
Requires spray nozzle which clogs easily therefore, plugging problems are associated with spray nozzles.	The elimination of spray nozzle reduces the complexity of the process and avoids the plugging (Sheskey 2008).
Requires more water to granulate, over wetted granules require long drying times.	No over wetting of granules, therefore less drying time, reduce manufacturing time (Tan et al. 2009).
Not useful for low dose, water sensitive and hydrophobic powders.	Have potential for granulating water sensitive drugs, low dose and hydrophobic powders (Sheskey 2008).

2. MATERIALS AND METHODS

The following materials were used as received. Drug Silymarin DPE (70%) was obtained as a gift sample from Maneesh Pharmaceuticals Private Ltd, Maharashtra, India. Lactose monohydrate (filler), Avicel PH-101 (dry binder), Sodium starch glycolate (disintegrant) and Magnesium stearate (lubricant) were provided by Arbro Pharmaceuticals Pvt. Ltd, New Delhi, India. METHOCEL E6 PLV (foam binder) was received as a gift sample from Colorcon Asia Pvt. Ltd. The equipments: Dissolution apparatus (DS 8000, Labindia Pvt. Ltd, India), UV Spectrophotometer, (Shimadzu 1601, Japan), Air compressor, Hardness tester (Strong-Cobb Pfizer and Schleuniger tester), Texture analyzer (Stable Micro Systems- Texture Exponent 32), Optical microscope (Motic Images 2000, B1 series), Brookfeild Viscometer (Spindle C50-1), Humidity chamber (Thermolab, India), Friabilator (Roche Friabilator), Disintegrator tester, Electronic balance (Scientific Systems, India), Spray gun (local make), disposable syringes, glass petriplates, double distilled water, and graduated measuring cylinder etc were used during the study.

2.1. Foam preparation and its assessment: Air from the compressor was passed through the aqueous binder solution to form foam through a spray gun. Concentrations of METHOCEL E6 PLV viz. 1%, 5%, 7% and 10% were used. All were evaluated for some potentially important foam properties.

***2.1.1. Optical microscopy*:** One drop of foam binder was placed on glass slide and observed for the size of air filled bubbles at 10X in an optical microscope (Tan et al. 2009).

2.1.2. Firmness analysis: The objective was to compare the consistencies of different foam binders by back extrusion technique which gives an indication of product physical failure and viscosity using texture analyzer. Tests were carried out in a standard size back extrusion container (50 mm diameter), approximately 75% full, and extension bar using 5kg load cell immediately after removal from storage at a specific temperature e.g. 25 ºC. The 35 mm extrusion disc was positioned centrally over the sample container. For comparisons of cohesiveness and work of cohesion the probes must return to the same position above the samples after each test. To do this the probe was calibrated to a distance of 30 mm, above the top of the container or sample surface (Cantor et al. 2009).

2.1.3. Viscosity: The foam viscosities were evaluated with the help of Brookfield viscometer at the room temperature (20 ºC) using the spindle C50-1 with the help of method reported in literature (Tan et al. 2009).

2.1.4. Density: The foam densities were calculated on an electronic weighing balance for accuracy with the help of reported method (Tan et al. 2009).

2.1.5. Foam Quality: It is equivalent to the gas volume fraction contained within the foam and was calculated with the help of a reported method (Tan et al. 2009) by using the formula where; V= volume of gas and volume of liquid.

$$FQ = \frac{V_{gas}}{V_{gas} + V_{liquid}} \times 100$$

2.1.6. Stability: The foam stability was assessed with the foam drainage characterization by keeping the foam in graduated measuring cylinder and calculated as the foam slowly collapses over time into liquid (Tan et al. 2009).

2.2. Mechanism of foam nucleation on loose powder bed: The study

of single nuclei formation on a small static silymarin powder bed was carried out for all foam binders and compared with a drop of water as "drop versus foam" and the penetration time and specific penetration time were calculated (Tan et al. 2009).

2.2.1. Penetration Time: It is defined as the time required for foam to completely penetrate into powder bed.

2.2.2. Specific Penetration Time: It is defined as the penetration time (tp) per unit mass of foamed binder (m) and is represented by:
Tp= tp/m

2.3. Granule formation and testing: Firstly, the nucleation ratio which is defined as the amount of powder nucleated per unit mass of liquid binder required (Tan et al. 2009) was calculated and granules so formed were evaluated for various parameters:
Km= Mn/Mb
Where, Mn and Mb are the nucleus mass and liquid binder mass respectively.

2.3.1. Bulk and Tapped Density
The density parameters were determined using a 100 ml graduated cylinder (n=3) with known amount of granules. The bulk and tapped density values were used for the calculation of Carr's Compressional Index and Hausner's Ratio (Banker and Anderson 1987).
HR = Tapped density/ Bulk densit

$$\%Compressib\ ility = \frac{Tapped\ \ density\ -\ Bulk\ \ density}{Tapped\ \ density} \times 100$$

2.3.2. Flowability (Angle of repose)
From angle of repose by the funnel method, the dynamic a for each batch of granule was determined (Banker and Anderson 1987)

2.3.3. Sphericity
The sphericity of the granules was measured by measuring length, width and radius of the granule using an optical microscope (Motic Images). The shape factor was expressed as % Sphericity, where 100% corresponds to a perfect sphere. The sphericity of approximately 20 granules from each batch was calculated (Pai et al. 2011).

2.3.4. Granule compressibility assessment using texture analyzer
The compressibility of foam granules using a 25 mm cylinder probe with 25kg load cell was done on texture analyzer. Before testing, the probe was calibrated against the machine base and returned to a set distance e.g. 3mm. Granule samples were placed diametrically on the machine base and position centrally under the probe. The compression was commenced and repeated for all granule batches (Cantor 2009).

2.4. Tablet evaluation
2.4.1. Hardness and Friability: Tablet hardness is physical strength measurement of the tablet defined as the force required to break a tablet by compression in the radial direction by hardness tester. Tablet friability was measured as the percentage of weight loss of 20 tablets tumbled in a friabilator. After 4 min of rotation at 25 rpm, the dust of tablets was removed and the percentage of weight loss calculated (Banker and Anderson 1987).

2.4.2. Diametrical crushing strength: It measures the force required to cause tablet failure and identifies important characteristics missed by conventional tablet hardness testers, which only measure the point force at which the tablet breaks. A high resolution texture analyzer was involved to study the failure behaviour of tablets due to diametrical compression using a 25 mm cylinder probe (P/25) using 25kg load cell and a testing speed of 0.03mm/s, post test speed 10.00 mm/s and distance 0.5 mm all that required for this application. Tablets were placed diametrically on the machine base and positioned centrally under the probe and compression test was commenced. The maximum force value, i.e. the peak, is the force required to initiate mechanical failure of the tablet followed by further breakdown. The greater the maximum force value the harder is the tablet (Cantor 2009). From the curves the radial and axial tensile strengths were determined from the formulas where; F is the peak compression force, d is the diameter of the tablet, t is the thickness of the tablet and ? ~ 3.147
Radial tensile strength = 2F / ? d t
Axial tensile strength = 4F/ ? d^2

2.4.3. Disintegration: The disintegration tests were performed at 37 ºC in double distilled water, using disintegrator tester (Banker and Anderson 1987).

2.4.4. Surface morphology: Studies were conducted with the help of an optical microscopy under 4X magnification for the assessment of tablet surfaces.

2.4.5 Drug release studies: Release studies were carried out for all foam bonded tablets and compared with direct compression silymarin (control) tablets using USP type II (paddle) dissolution apparatus (Hussein et al. 2012). The dissolution medium consisted of 900 ml of double distilled water in a dissolution flask maintained at temperature of 37± 0.5 ?C and 100 rpm. One silymarin tablet from each set was placed in the dissolution apparatus and the test was allowed to run for 120 minutes. Samples measuring 10 ml were withdrawn at suitable intervals and replaced with fresh dissolution medium to keep constant volume. Collected samples were filtered with syringe filters (Millipore 0.5 um) and the filtrate was diluted with blank dissolution

medium and analyzed spectrophotometrically at 288 nm using distilled water as blank. From the dissolution data percentage drug release as a function of time in minutes was calculated.

2.4.6 Drug release kinetics: To analyze the mechanism of drug release kinetics from the dosage forms, the dissolution data so obtained were fitted in all release models and the model with the highest correlation coefficient was considered to be the best fit model (Costa and Lobo 2001).

2.4.7 Stability Studies

The accelerated stability study was performed for the optimized formulation of foam bonded silymarin IR tablet by loading it in the stability chamber at 45 ± 2 ºC and 75% ± 5% relative humidity for a period of three months. Upon completion of the stability study, the samples were evaluated for physical characteristics; drug content and dissolution profile (Pai et al. 2011).

3. RESULTS AND DISCUSSION

3.1. Design of silymarin tablets by novel Foam Granulation Technique

Silymarin, the active component of *Silybum marianum* plant also known as milk thistle, is a standardized extract consisting of approximately 70% to 80% silymarin flavonolignans (mainly silybin A and B, isosilybin A and B, silydianin, and silychristin. It is a gold standard drug for the treatment of liver and gallbladder disorders, including hepatitis, cirrhosis, jaundice etc. But the oral bioavailability of silymarin is hampered by its low water solubility and poor dissolution characteristics (Javed et al. 2011). *The Foam Granulation Technique* was thus employed to prepare silymarin IR tablets on the laboratory scale by using Methocel E6 PLV as foam binder in various concentrations *viz.* 1%, 5%, 7% and 10% for the dissolution enhancement and evaluated for all tablet parameters like drug content, hardness, friability, weight variation, disintegration and dissolution profiles (Keary and Sheskey, 2004; Sheskey et al. 2004; Sheskey et al. 2006; Sheskey 2008 and Do et al. 2008). All powders, except magnesium stearate were mixed properly for 1 min to achieve a uniform mixture before the next agglomeration step. Foam binder was then incorporated to the powder mixture and after proper mixing the dough was sieved through sieve number 12 for the formation of granules. The granules were dried and then lubricated and compressed as tablets as explained schematically in Figure 1. The compression of the formulation after the milling step can be accomplished using any tablet press. Here, the compression step was carried out using a 10 station rotary tablet press (Camag, Japan).The formulation was inserted into the die and was subsequently press-molded. The compression force can be selected based on the type/model of press, physical properties as desired for the tablets product.

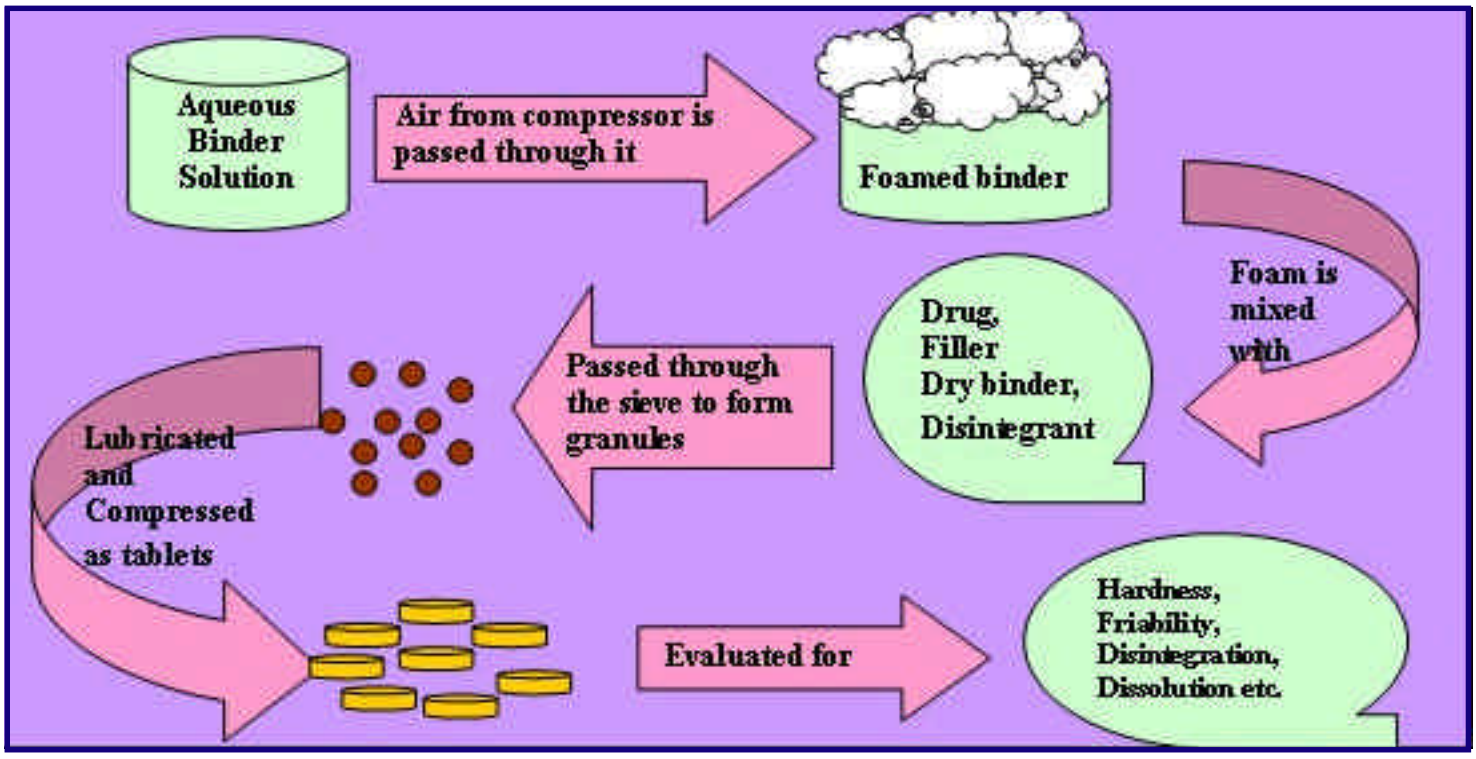


Figure 1. Schematic representation of foam granulation technology.

3.2. Technological Properties of the Foam Binder

3.2.1. Optical microscopy

The photomicrographs showed that the 1% foam had small air filled spaces completely packed with each other with less of liquid in it; 5% foam the size of air filled spaces increased a bit, whereas in 7% and 10% foam large air filled spaces were observed with more liquid present (Figure 2).

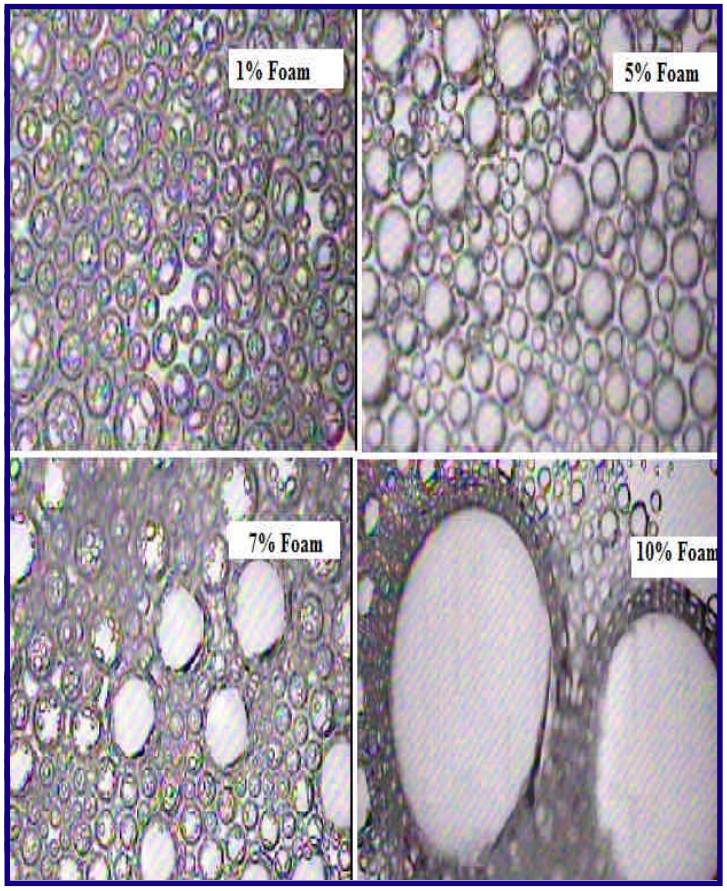


Figure 2. Photomicrographs of various foam binder concentrations showing an increase in the air vacuole sizes from 1% to 10% as observed by an optical microscope.

3.2.2. Firmness analysis of foam by texture analyzer

When a 10 g trigger was attained (i.e. point at which the disc's lower surface was in full contact with the product) the disc proceeds to penetrate to a lower depth of 30 mm. At this point (the maximum force), the probe returns to its original position. The peak or maximum force is taken as a measurement of firmness – the higher the value the firmer is the sample. From the curves obtained, the firmness increased with increase in concentration of foam binder i.e. 10% foamed binder exhibited greater firmness as compared to other lower concentrations [Figure 3a-d).

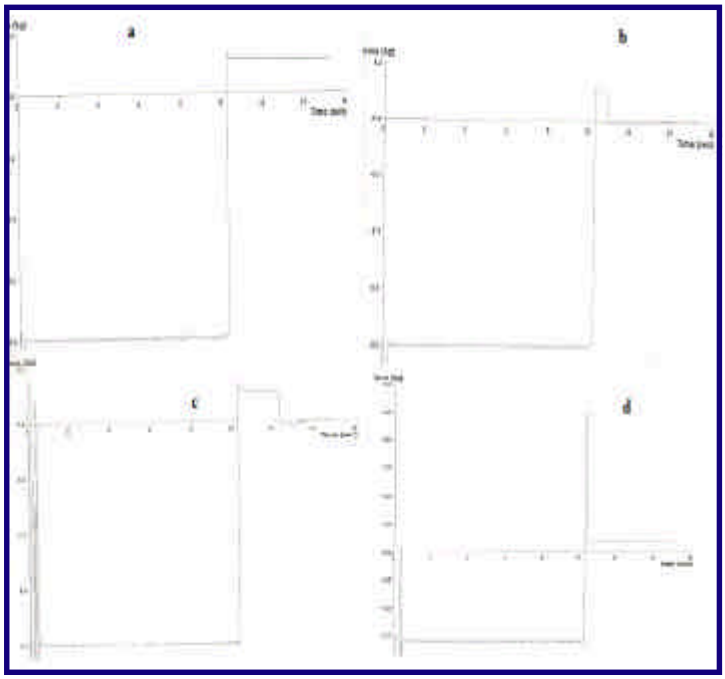


Figure 3. Texture analyzer graphs showing foam firmness in 1%, 5%, 7% and 10% concentrations in a, b, c and d respectively.

3.2.3. Other potential foam properties

The viscosity, density and stability of foam binder were found to increase proportionally with binder concentration. The foam stability findings were concordant with those described in literature as increasing viscosity of the liquid from which foam is prepared decreases the drainage rate of foam and stabilizes the foam (Pugh 1996). Therefore, the foams of less viscous solutions (1% and 5%) were found to be unstable as compared to highly viscous solutions (7% and 10%). The foam quality was found to decrease with increase in binder concentration. Lower viscous solutions were easy to foam and resulted in very high quality foam (Table 2). The findings were in accordance with those mentioned by Tan et al., 2009. These potential properties of foam binder helped us in deciding the appropriate foam concentration to be used in the further experiments.

Table 2. Properties of the various Methocel E6 PLV foam binder

Foam binder (Methocel)	Viscosity (mPas)	Force "firmness" (kg)	Density (g/ml)	Stability (minutes)	Foam Quality (%)
1%	15.360	0.08	0.99	2	90% (high)
5%	17.115	0.16	1.01	5	85%(medium)
7%	26.489	0.18	1.08	8	78% (low)
10%	40.758	1.25	1.10	10	66% (low)

3.3. Mechanism of foam nucleation on loosely packed powder beds

Tan and Hapgood 2010, proposed two mechanisms of wetting and nucleation for foam granulation: "*foam drainage*" controlled regime and "*mechanical dispersion*" controlled regime. In the "*foam drainage*" mechanism, the controlling property is the foam drainage. The

liquid in foam drains into powder bed and forms nuclei. In "*mechanical dispersion*", powder mixing dominates the wetting and nucleation mechanism, foam drainage has a minimal effect.

Thus, the purpose here was to find out the foam nucleation mechanism for which different static powder beds of silymarin were prepared by sieving the silymarin DPE into petri dishes and the bed surface was scraped smooth using a spatula. Methocel E6 PLV: 1%, 5%, 7% and 10% were used in foam penetration kinetics which was compared with penetration of a drop of water on powder bed (Tan and Hapgood 2010). It was found that the water drop followed the *drop controlled nucleation regime*, as the drop landed on the powder surface it rolled over the powder bed because of hydrophobic nature of silymarin (Figure 4) and after a period of 10.5 minutes it penetrated into the powder bed and formed puddle as shown schematically (Figure 5), no liquid marble was formed confirming the amorphous nature of silymarin powder and ruling out the "*solid-spreading" nucleation mechanism* as described by researchers in granulation of hydrophobic powders (Hapgood and Khanmohammadi 2009). The foam drops followed the *foam drainage controlled regime* and penetration time and specific penetration time were found to increase with increase in concentration. This may be due to the prolonged time needed for the coalescence of foam bubbles and liquid drainage to induce liquid penetration into powder bed from higher foam concentration 7% and 10%, since the amount of liquid is more as compared to air, at this stage it can be stated that increasing the viscosity slows down the velocity of liquid penetration into the silymarin powder bed. Also, higher the foam quality less is the penetration time and vice versa (Tan and Hapgood 2010). The penetration time of all the foam binders was short as compared to water drop and liquid drainage, one of the characteristics of foam, was found to play a vital part in the mechanism of foam imbibition into silymarin powder bed (Table 3). It was also noticed that foam resulted in less saturated nuclei formation whereas water drop resulted in highly saturated nuclei formation.

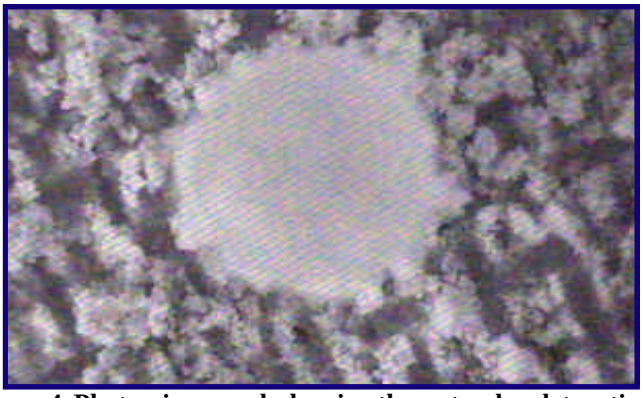


Figure 4. Photomicrograph showing the water droplet resting on silymarin dry powder bed at the magnification 4X by an optical microscope.

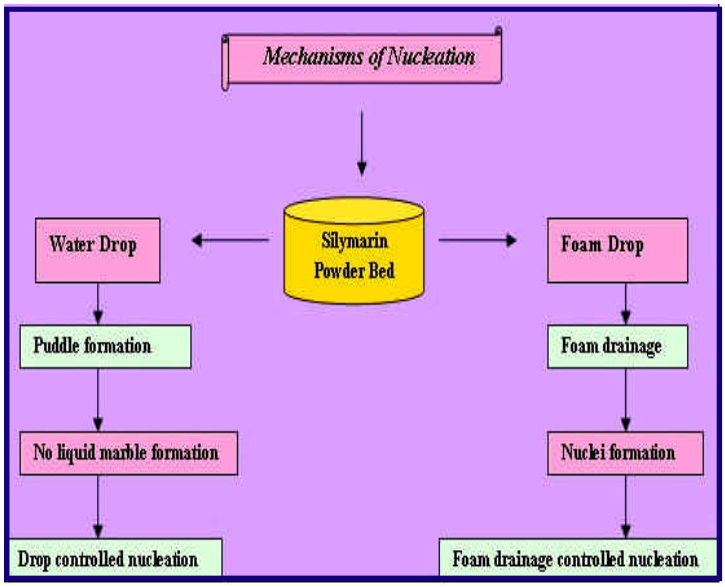


Figure 5. Schematic representation of nucleation mechanism on silymarin powder bed.

Table 3. Penetration time and specific penetration time of foam vs. water on silymarin powder bed.

Penetrant	Penetration Time (t_p) (minutes)	Specific Penetration Time (T_p) (minutes)*
1% Foam	2.0	2.02
5% Foam	4.2	4.15
7% Foam	7.4	6.85
10% Foam	8.6	7.81
Water drop	10.5	10.5

** $T_P = t_p/m$ (where, m = density of foam)*

3.4. Nucleation Ratio

After assessment of foam properties and its mechanism of penetration on loosely packed silymarin powder bed, the nucleation ratio was evaluated. When binder is brought in contact with powder, the particles are nucleated by the fluid to form granules. The efficiency of foam nucleation in terms of the mass of nuclei formed per unit mass of fluid added is addressed by the nucleation ratio (Tan et al. 2009; Tan and Hapgood 2010). Here it was seen that increasing the binder concentration increased nuclei mass proportionally and nucleation ratio almost doubled (1 gram of 1% foam produced nuclei mass of 1.2 g whereas 1 gram of 10% foam produced 2.4 gram of nuclei). This can be attributed to the fact that 10% foam have large amount of liquid in it which can granulate more powder mass into granules. The data in Table 4 confirmed the influence of foam quality on nuclei formation and a larger nucleation ratio of foam compared to water indicated that foam granulation method provides better liquid distribution within the powder bed to form granules. These readings were in accordance with those reported in literature (Tan and Hapgood 2008).

Table 4. Foam nucleation ratio and granule rheological properties

Parameters	Granule Rheology			
	1% Foam	5% Foam	7% Foam	10% Foam
Nucleation ratio	1.2	1.6	2.0	2.4
Bulk density (g/ml)	0.53	0.48	0.45	0.40
Tap density (g/ml)	0.63	0.58	0.56	0.54
Compressibility (%)	15.45	17.25	20.65	25.95
Hausner's Ratio	1.16	1.18	1.24	1.35
Angle of repose	26.8	28.5	32.0	34.3
% Sphericity	~0.72	~0.80	~0.65	~0.60
% Compressibility vs. Flowability	Excellent flowability properties as the value lied b/w 5-15	Good flowability as the value lied b/w 12-16	Fair flowability as the Value lied b/w 18-21	Poor flowability as the Value lied b/w 23-35
5-15 Excellent				
12-16 Good				
18-21 Fair				
23-35 Poor				
33-38 Very poor				
<40 Extremely poor				

3.5. Evaluation of granule technological properties

3.5.1. Rheological properties

The Carr's and Hausner's Indices were used to indicate a powder's flow properties. Lower the value, the more free flowing is the powder. Carr's Index (CI) values below 20% are considered to have good to free flowing properties. Similarly, Hausner's Index (HI) values less than 1.22 are associated with moderate to excellent flow. The angle of repose is also used to indicate a powders flow and values less than 30° represent materials with good flow properties (Banker and Anderson 1987). It is well known that the selection of appropriate polymeric binder to be used to agglomerate drug with excipients is a critical issue in pharmaceutical tablet development process. Therefore, a crucial step is the choice of the most appropriate drug/excipient/binder ratio to enhance the formation of liquid bridges between all the solid species and hence, that of granules, upon which other tablet parameters will rely (Simons et al. 2005). From the results (Table 4) it was seen that the flow properties of the granules decreased as binder concentration increased. This can be attributed to presence of considerable amount of fines present in 1% granules as compared to other binder concentrations. The 1% and 5% Methocel E6 PLV bonded granules were less saturated, as less liquid bridges were formed in between them because of fewer amounts of water and more amount of air in the foam from which they were granulated. They had a narrow size distribution with weak nuclei which easily broke into fines Whereas, the granules 7% and 10% Methocel E6 PLV were highly saturated because of strong liquid bridges formed between them because of large amount of water in the foam from which they were granulated; they were coarser with wide size range distribution and irregular in shape as shown in Figure 6. The granules formed from 5% Methocel E6 PLV were found to be of optimum quality and characteristics especially in terms of sphericity (Figure 7) concluding the fact that medium FQ was optimum for the formation of proper spherical granules of silymarin DPE with appropriate granule rheology.

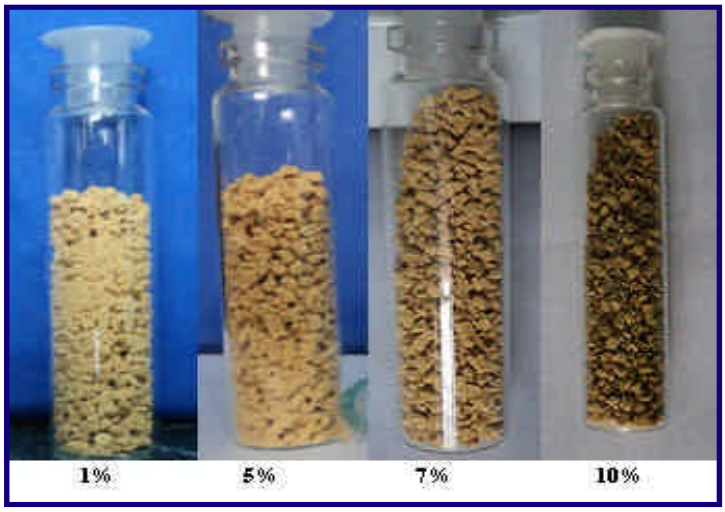


Figure 6. Granule batches prepared from different binder concentrations.

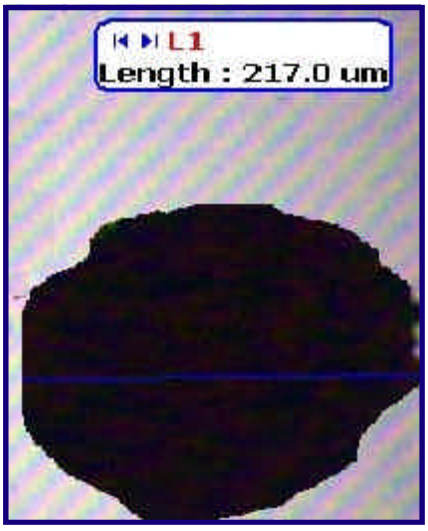


Figure 7. Sphericity of 5% Methocel E6 PLV bonded granule.

3.5.2.Granule compressibility assessment using texture analyzer

From the texture analyzer curves for granule compressibility, it was seen that on contact with the sample a rise in force was observed as the probe continues to compress the sample. This rise in force continues until the probe has moved down 2.5 mm, point at which the granules have been compressed. The probe then proceeded to return to its initial starting point. The maximum force "hardness" of the samples were 0.68, 2.60, 6.25 and 6.25 kg for 1%, 5%, 7% and 10% granules respectively (Figures 8a-d) confirming the formation of less liquid bridges in high FQ (1%), increase in hardness was observed in medium FQ (5%), and maximum hardness in low FQ (7% and 10%). Thus FQ was found to play a vital role in granule strength.

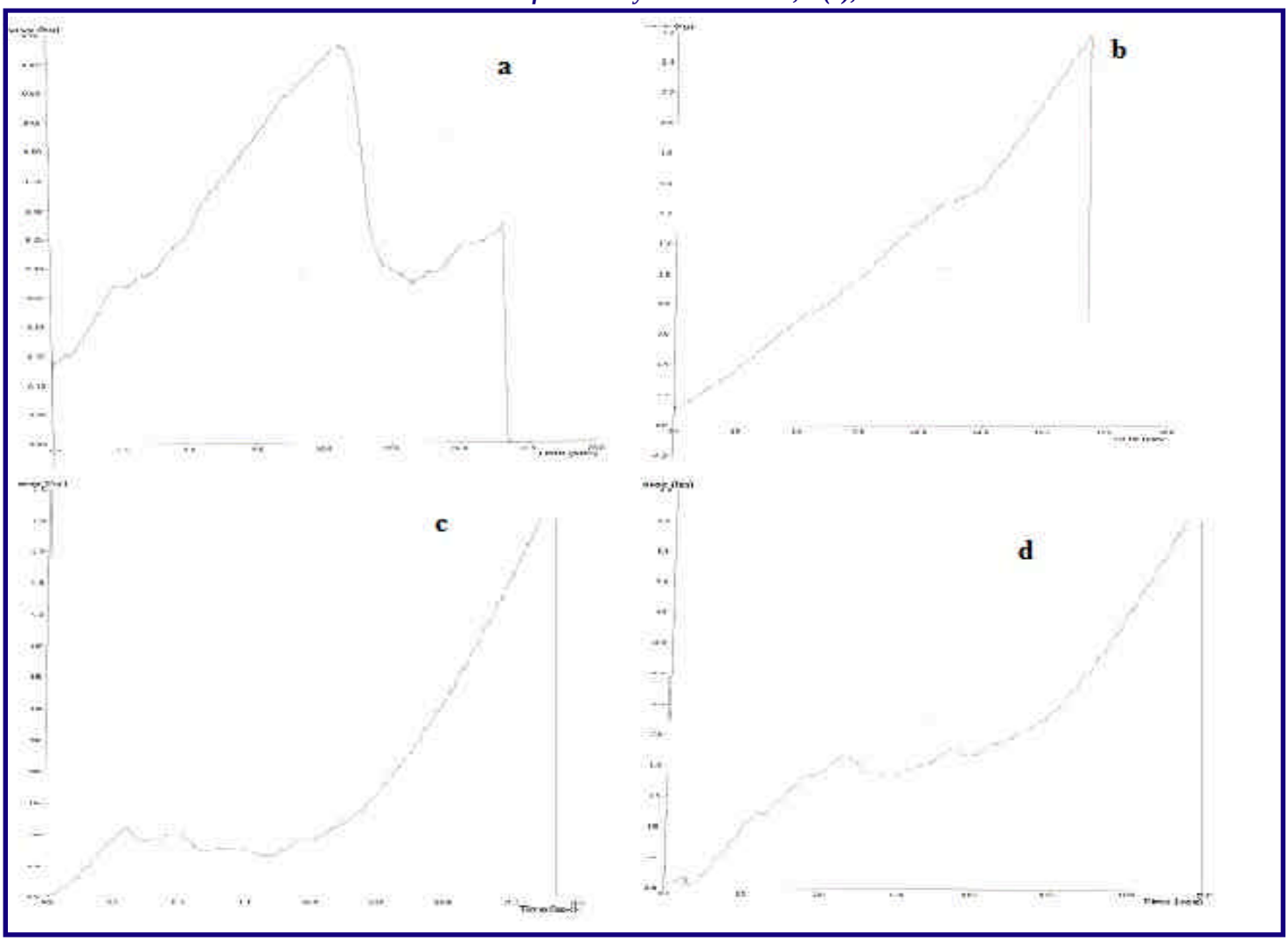


Figure 8. Compressibility behavior of 1%, 5%, 7% and 10% foam bonded granules using texture analyzer.

3.6. Silymarin foam tablet evaluation

After sufficient foam binder analysis and granule rheology, the four prototype foam bonded IR tablets of silymarin were formulated and compared with direct compression tablet as control (Figure 9) (Table 5) and were evaluated for all tablet parameters (Soares et al. 2005). In a previous study conducted by the authors, the solid state compatibility between silymarin DPE and various tablet excipients by thermal and non-thermal methods showed compatibility between the drug and excipients used here (Javed et al. 2012).

3.6.1. Hardness and Friability: Hardness increased with increase in Methocel E6 PLV foam binder concentration from 1% to 10% and this showed that binder played a direct/proportional role in tablet hardness (Table 5). The postulated theory behind this was that granules formed from 1% and 5% were less hard because of fewer liquid bridges in them whereas, 7% and 10% foam binder produced a large extent of

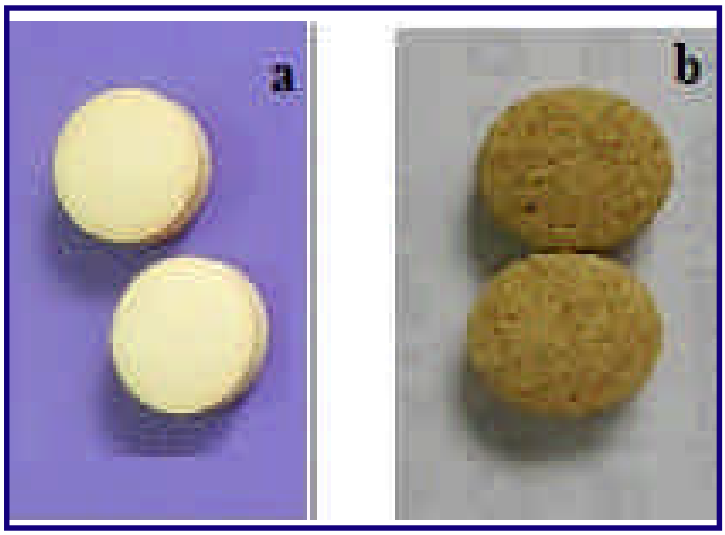


Figure 9. IR tablets of silymarin (a) control by direct compression (b) bonded with 5% Methocel E6 PLV as foam binder.

Table 5. Silymarin IR foam bonded prototype formulations

Ingredients (mg)	Formulation codes				
	Control	F1	F2	F3	F4
Drug (eq. to 140 mg of silymarin)	200	200	200	200	200
Lactose (filler)	35	35	35	35	35
Avicel pH 101 (binder)	50	50	50	50	50
SSG (4%) (disintegrant)	12	12	12	12	12
Magnesium stearate (1%) (lubricant)	3	3	3	3	3
Methocel E6 PLV (foam binder) q.s*	0%	1%	5%	7%	10%
Tablet weight (mg)	305.5±3.0	304.8±2.92	303±3.01	303±3.26	304±3.94
Drug content	98.7±0.55	99.70±0.54	100.0±0.98	100.0±0.32	98.9±0.412
Diameter (mm)	8.2±0.16	8.1±0.26	8.3±0.21	8.2±0.17	8.1±0.14
Thickness (mm)	2.1±0.11	2.2±0.10	2.1±0.06	2.2±0.05	2.3±0.16
Radial tensile strength (MN/m^2)	0.189	0.230	0.414	0.505	0.710
Axial tensile strength (MN/m^2)	0.085	0.115	0.200	0.265	0.360
Hardness (kg/cm^2)	4.25±0.55	6.8±0.34	10.5±0.53	13.5±0.28	18.0±0.67
Friability (% w/w)	1.08	0.50	0.35	0.15	0.04
Disintegration (min)	1.1±0.33	5.0±0.24	6.5±0.33	7.8±0.45	10.0±0.48
Inference	*Tablets after initial evaluation parameter were tested for dissolution profiles and optimized formulation was kept for stability studies.*				

**** q.s – quantity sufficient , Values are mean ± S.D of tablets (n=6)***

wetting and nucleation, giving the largest fraction of very strong nuclei. The formulation F2 with 5% Methocel E6 PLV was considered appropriate with hardness of 10.5 kg/cm^2. Also harder the tablets, less was the % friability i.e. hardest formulation with 10% foam binder was found to least friable (Figure 10).

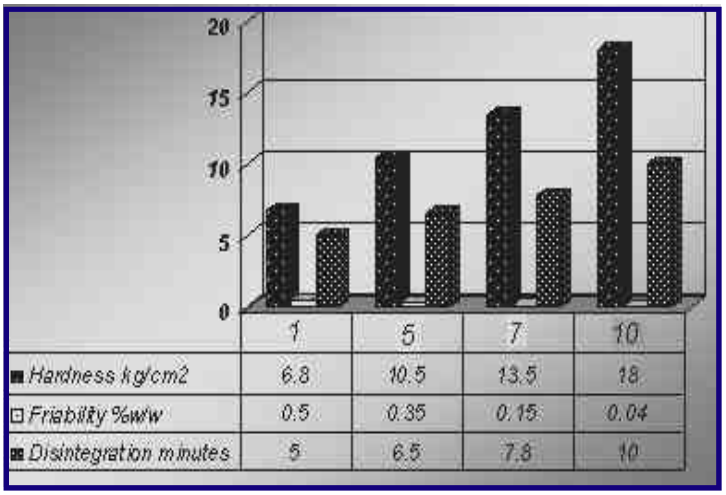


Figure 10. Graph showing the effect of Methocel E6 PLV (1%, 5%, 7% and 10%) on hardness, friability and disintegration of foam bonded silymarin IR tablets.

3.6.2. Disintegration: Disintegration time doubled as binder concentration increased from 1% to 10%. Therefore, harder the tablet, prolonged will be the disintegration time. The 5% bonded tablet formulation took 6.5 minutes for complete disintegration (Table 5).

3.6.3. Diametrical crushing strength: In F1 tablet with 1% foam binder, the maximum force required to break the tablet was 6.0 Kg followed by further breakdown within 23 seconds. Whereas, F2 with 5% foam binder broke at 10.5 Kg and F3 with 7% foam binder at 13.5 Kg and F4 with 10% foam binder at 18.0 Kg. No crack propagation was observed in these tablets. From the curves obtained with the help of texture analyzer, the radial and axial tensile strengths were determined as shown in Table 5.

3.6.4.Tablet surface morphology: The tablet surface morphology studies of Methocel E6 PLV bonded foam tablets F1 – F4 were preformed with the help of optical microscopy under 4X (Figure 11). One important observation was that foam tablets contain large fissures, pores and voids at their surface. The reason may be the principle of nucleation by foam drainage leading to granules with pores and voids filled with air and then simultaneous release/venting of entrapped air through the tablet surface. The F1 with 1% foam binder had bigger pores and pore size decreased in other formulations. Relatively smooth surface was observed in F4 formulation showing greater compaction.

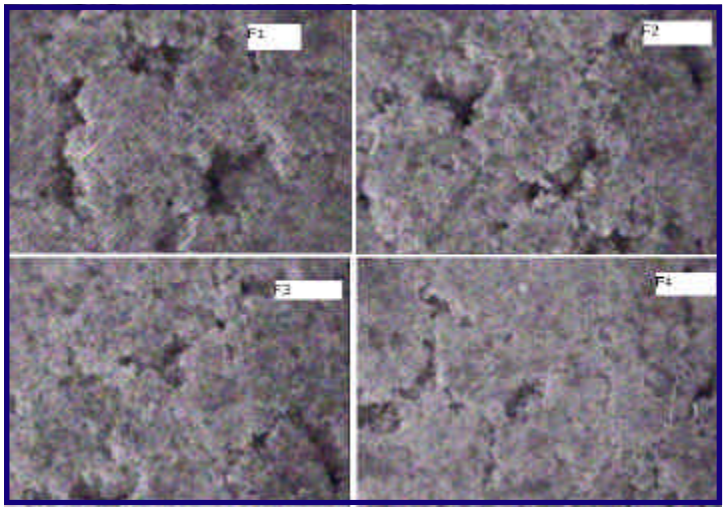


Figure 11. Surface morphology photomicrographs of the foam bonded tablet showing big fissures in F1 and the fissure size decreased with F2, F3 and F4 at the magnification of 4X by an optical microscope.

3.6.5. Dissolution studies of foam bonded silymarin tablets

The uncoated direct compression tablet of silymarin DPE (control) and the foam bonded silymarin tablet formulations (F1 – F4) were tested for comparative dissolution profiles with % drug release as a function of time (minutes) to study the effect of Methocel E6 PLV on the dissolution of silymarin in distilled water (pH 6.5). The dissolution parameters were set as shown in Table 6.

Table 6. Dissolution parameters set up

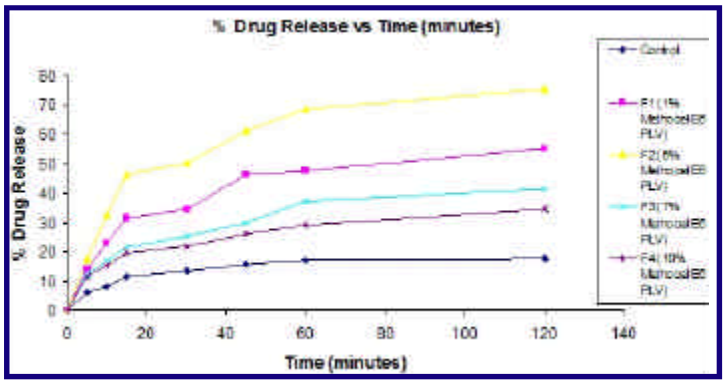
System	Conditions
Agitation system	USP II (Paddle) type
Stirring rate	100 rpm
Dissolution medium	Double distilled water (pH 6.5) (Ningyun et al 2008)
Medium volume	900 mL
Detection method	UV spectroscopy at 288 nm (Campodonico et al. 2001)
Sampling time	120 minutes

As determined previously, the solubility of silymarin in double distilled water was found to be 0.05mg/mL (Javed et al. 2012), thus there was a need to modulate the dissolution profile of silymarin by using foam binder Methocel E6 PLV in varying concentrations so that dissolution profile ideal for immediate release tablets could be obtained. From the results (Table 7); it was seen that the dissolution rate of silymarin control tablets in distilled water was limited, with a total of less than 20% drug release after 120 minutes and the results complied with the fact that plain silymarin does not show good dissolution characteristics. Whereas, in the foam tablets (F1– F4) enhancement in dissolution rate was observed in all with % drug release of about 55.1 % with 1% Methocel; 75.5 % with 5% Methocel; 41.3% with 7% Methocel and 34.5% with 10% Methocel concentration at 120 minutes (Figure 12). The dissolution rate enhancement of the silymarin foam bonded tablets containing 1% and 5% Methocel E6 PLV was due to the surfactant effect of Methocel E6 PLV for poor solubility drugs. The best dissolution profile was observed in F2 foam tablet formulation, when Methocel E6 PLV (5%) released 75.5 % of silymarin in 120 minutes, ideal for immediate release tablets. At the higher Methocel E6 PLV concentrations, it is suggested that the dissolution slowing effects of polymer gelation and polymer-polymer chain entanglement offset the surfactant properties imparted by the polymer concluding to the fact that dissolution rate decreased with increasing concentration of Methocel E6 PLV upto 7% and 10%. The slow down effect of Methocel E6 PLV also depends on the water solubility characteristics of the drug i.e. lower water solubility drugs had slower dissolution rates at the highest Methocel E6 PLV concentrations (Do et al. 2008). Also the effect of Methocel as a foam binder was found to be more significant with tablets containing low water solubility drugs with the higher concentration as in case of silymarin here. Amongst all the silymarin foam bonded tablets 5% Methocel E6 PLV showed the best dissolution profile for silymarin tablets ideal for immediate release tablets with about $T_{20\%}$, $T_{50\%}$ and $T_{75\%}$ drug release in 5, 30 and 120 minutes respectively. The % drug release from F2 formulation bonded with 5% Methocel was fitted in various release models and was found to fit in Higuchi model "Fraction DR vs. Square root of time" with $R^2 = 0.8831$.

Table 7. Drug release from direct compressed tablets vs. foam bonded tablets.

Time (minutes)	% Drug Release Control tablet (direct compression)	F1	F2	F3	F4
0	0	0	0	0	0
5	6.05	14.2	17.6	12.2	11.5
10	8.18	22.9	32.7	16.7	15.2
15	11.6	31.4	46.2	21.3	19.4
30	13.5	34.5	50.3	25.4	21.8
45	15.6	46.2	61.3	30.0	26.4
60	17.4	47.3	68.6	37.1	29.2
120	17.6	55.1	75.5	41.3	34.5
$T_{20\%}$ (minutes)	—	10 min	6 min	15 min	30 min
$T_{50\%}$ (minutes)	—	120 min	30 min	—	—
$T_{75\%}$ (minutes)	—	—	120 min	—	—

$T_{20\%}$ is time for 20% of release



4. Conclusion

In this study, an initial evaluation of the feasibility of Foam Granulation Technology on IR tablets of silymarin was conducted on laboratory scale by using Methocel E6 PLV as a granulation binding agent for immediate-release tablet and capsule products. The Methocel E6 PLV bonded tablets provided optimum friability, hardness and disintegrating times followed by dissolution enhancement owing to its surfactant effect. The 5% Methocel bonded formulation was found to be superior from direct compression formulation in all aspects. The accelerated stability study revealed that optimized foam tablet showed no significant change in appearance, physico-chemical properties and dissolution profiles upto a period of 3 months. Such silymarin tablets can be used for commercial use but considering the laboratory scale, our study was based on the formation of single nuclei in a static powder bed, which is expected to be vastly different to the dynamic conditions in a high shear mixer granulator where shear forces are presumed to be sufficient to cause deformation and destruction of the nuclei. Also, the interactions of binder and powder particles in a high shear mixer granulator are complex in nature and

this may affect the binder dispersion and nucleation mechanism and subsequent granule formation on manufacturing scale.

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Declaration of Interest

The authors report no declaration of interests

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