



Chaw, Cheng, Ting, Grace Loong and Chan, Yen Yee (2019)
Mixed solvent system as binder for the production of silicified
microcrystalline cellulose-based pellets. *Journal of Applied
Polymer Sciences*. ISSN 0021-8995

Downloaded from: <http://sure.sunderland.ac.uk/id/eprint/10839/>

Usage guidelines

Please refer to the usage guidelines at
<http://sure.sunderland.ac.uk/policies.html> or alternatively contact
sure@sunderland.ac.uk.

Mixed solvent system as binder for the production of silicified microcrystalline cellulose based pellets

Ting, Grace Loong; Chan, Yen Yee; Chaw, Cheng Shu*. University of Sunderland, Faculty of Health Sciences and Well Being, Department of Pharmacy and Pharmaceutical Sciences, City Campus, Sunderland, United Kingdom, SR1 3SD.

*corresponding author (Email: Cheng.chaw@sunderland.ac.uk)

ABSTRACT Silicified microcrystalline cellulose pellets with hydroxypropyl methylcellulose (HPMC) as modifier were prepared using a mixed solvent as liquid binder. Pellets were produced using extrusion-spheronization with a mixed solvent consisting of water and isopropanol as liquid binder. The key spheronization aid was Prosolv® SMCC 90. Low viscosity grade HPMC was incorporated aiming to modify release of indometacin. Physical characteristics including breaking load, apparent density and flow properties, particle size distribution and shape were determined. Drug loaded pellets were also tested for dissolution profiles. By adjusting liquid binder property, at isopropanol to water ratio of 3.5 to 6.5, pellets of desirable size and shape with reasonable yields were obtained. Pellets exhibited good flow property and they were mechanically strong. Pellet with higher HPMC content displayed a faster drug dissolution profile. This was because low viscosity grade HPMC was not enough to create strong gel. Instead hydration of HPMC molecules increased matrix's hydrophilicity and weakened the structure of pellet faster. The release of indometacin was partly based on the erosion of hydrated matrix. The presence of HPMC in the pellets would require a mixed solvent to produce desirable shape. Incorporation of HPMC had modified drug release from the pellets without further coating.

1. INTRODUCTION

Extrusion-spheronization is a conventional technique to manufacture pellets. To form pellets by these techniques, microcrystalline cellulose (MCC) has been chosen as a spheronization aid as it can provide necessary plasticity to the wet mass¹. As MCC pellets have limited disintegration, it retards drug release to some extent². Conventional MCC such as Avicel PH101 has small size with relatively poor flow property³ while Prosolv® SMCC, a co-processed silicified MCC (SMCC) displays a better flow property⁴. An optimal elasticity of Prosolv® SMCC based wet masses can be produced⁶ and Prosolv® SMCC 50 has been used as an alternative aid to produce round pellets⁷. Prosolv® SMCC 90 has been selected as the key spheronization aid which has not been studied. The mean size of Prosolv® SMCC 90 is doubled of SMCC® 50⁴. As size of

MCC is known to affect pellet properties⁸, this will be explored in this study. Hydroxypropyl methylcellulose (HPMC) is a type of cellulose ethers⁹. It has been used as a tablet binder, a thickener and a film former. Besides, it is one of the key excipients in the modified release delivery systems. HPMC E5 based matrix began to swell when immersed in the fluid and HPMC molecules were plasticized to form hydrogel at the outer surface of the matrix¹⁰. The resultant structural transformation had led to changes in drug concentration at interface of the medium and glassy matrix limiting drug release. Generally speaking, rate of drug release from such systems is governed by the properties of HPMC including composition of substituent groups and particle size. One of the interesting factors is the viscosity of HPMC. Matrices consisting of HPMC grade with low viscosity exhibited higher drug release than those with high viscosity. As low oral bioavailability of water insoluble drug is an issue, HPMC has also been used as a dissolution rate-enhancing polymer¹¹. In our work, two different viscosity grades of HPMC will be used. They are HPMC 80-120cp¹³ and Methocel™ E15 LV (12-18cp for a 2% solution at 20°C)¹⁴. They are low molecular weight HPMC and are added to alter the properties of pellets and to modulate drug release. Water is the most common liquid binder employed in extrusion-spheronization and the effect of liquid binders on the MCC wet masses was studied¹⁵. As ethanol could not solvate MCC polar groups as water, ethanol molecules were readily removed by compression and produced wet mass with little cohesion. Because pellets were not successfully formed for water based HPMC wet mass, isopropanol (IPA), a class 3 solvent, has been used instead¹⁶. Water-IPA mixture is a solution as HPMC is insoluble in IPA, and has been used recently¹⁷. Pellets produced with organic solvents or mixed solvent systems possessed some non-classical features of MCC pellets¹⁸⁻¹⁹. For example, pellets produced with 40% IPA in water as liquid binder gave a complete disintegration and rapid dissolution, while the use of 4.9mol% ethanol with water has resulted in pellets with no pore and dense surfaces²⁰. Also the incorporation of HPMC has led to film rupture, which is not desirable¹⁷. Thus, the use of mixed solvents should be evaluated to reach the required attributes. Indomethacin (IND) is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and anti-inflammation actions. The dosage forms present in the current market are suppositories and capsules where the modified release oral preparations were coated. However, the patients who take conventional forms of indometacin are more likely to experience its associated side effects. Thus, the development of sustained release pellets containing indometacin can be advantageous²¹. Indometacin is practically insoluble in water²². Emcompress® is a free flowing form of dibasic calcium phosphate dihydrate (DCP) that is non-hygroscopic²³. It is used as a substitute to the drug in order to obtain the optimal formulation compositions and process conditions for

pellet production before loading of drug. In summary, we will explore the feasibility of combining HPMC and Prosolv[®] SMCC 90 to prepare pellets by extrusion-spheronization with the provision of these materials to modify dissolution profiles of indomethacin without the need of film coating. Our preliminary study will look at effect of altering ratios of IPA/water and pellet quantitative compositions which include amount and grades of HPMC, amount of silicified MCC (Prosol[®] SMCC 90) and DCP (drug substitute to produce blank pellets). The pellet quality will be examined in terms of size distribution, sphericity, flow behavior, mechanical property and drug dissolution. We will prepare Prosolv[®] SMCC 50 pellets (as control) and compare their physical properties to those made from Prosolv[®] SMCC 90, the key spheronization aid used. By using a mixed solvent as the liquid binder, this will ease processing of pellets with HPMC by extrusion-spheronization. Also adding HPMC will change pellet properties including the drug release profile.

2. MATERIALS AND METHODS

2.1 Materials

Prosol[®] SMCC 50, Prosolv[®] SMCC 90 and dibasic calcium phosphate dihydrate (Emcompress[®]) were obtained from Mendell, Penwest Pharmaceutical Ltd. (Surrey, UK). Isopropanol, HPMC with viscosity of 80-120cp and indometacin were obtained from Sigma Aldrich Company Ltd. (Dorset, UK). Methocel[™] E15 LV (abbreviated as HPMC 12-18cp) was obtained from Colorcon (Dartfort, UK). Water was freshly prepared distilled water.

2.2 Production of pellets

Pellets were produced with Prosolv[®] SMCC 90 and HPMC 80-120cp and DCP via extrusion-spheronization. Prosolv[®] SMCC 50 and Methocel[™] E15 LV were also used as alternative aid and hydrophilic polymer, respectively. The optimal formulation compositions were loaded with 10% drug replacing DCP. Water or water-IPA was used as liquid binder. The suitable amounts of these dried ingredients were weighed (Precisa Balance Ltd., Dietikon, Switzerland). Total dried powder content for each batch was 60g. The powders were pre-mixed using Turbula Mixer (TC-2, Willy A. Bachofen AG, Basel, Switzerland) for 3 minutes at 45rpm. Then, the mixture was mixed in the planetary mixer (Model A901E, Kenwood Chef, UK) for 8 minutes with the speed setting of 3 and an appropriate amount of liquid binder which was almost equal to the amount of silicified MCC was added. Then the wet mass was extruded immediately with a radial extruder (Model 20 Extruder, Caleva Ltd, UK) that was fitted with a screen of 150mm in diameter and 1.0mm die holes. The extruder screen rotated at 30rpm. After storing the

extrudates in an air-tight container for 15 minutes, the sample was spheronized for 10 minutes (Model 120GB spheronizer, Caleva Ltd., UK) that was fitted with a 125mm cross-hatch frictional plate. Spheronization speed for screening purpose was been adjusted from 800 to 3000rpm. Ultimately, the remaining formulations were spheronized at 3000rpm. Pellets were collected and left to dry at 40°C oven until constant mass had reached. Table 1 listed the compositions of pellets.

2.3 Particle size distribution

Sieve analysis was conducted to assess size distribution of the pellets. A stack of British Standard sieves of $\sqrt{2}$ progression between 0.212 and 2.00mm was used. The pellets were poured into the top sieve and they were vibrated for 10 minutes using a sieve shaker (Model: EFL 2000, Endecotts Ltd., UK). After the shaking has completed, the mass of each sieve with retained pellets was determined in order to calculate the percentage of pellets retained of each sieve before constructing the frequency distribution. The percentages of coarse (>1.4mm) and fine fractions (<0.50mm) of the pellets were determined. According to the cumulative percentage size distribution curve constructed, the median diameter (D_{50}) and the interquartile range (IQR) were determined. IQR was determined by subtracting the sizes at the 75% cumulative frequency to the 25% cumulative frequency. The percentage yield was calculated based on the sum of pellet sizes between 0.5 and 1.4mm.

2.4 Pellet shape

An image analysis system (KS 400 version 3.0, Carl Zeiss Vision GmbH, Germany) was used to determine the 2D shape of pellets. Thirty pellets were randomly selected (sieve fraction: 0.71-1.0mm) for analysis. Pellets were placed under a pre-calibrated microscope (Leitz Dialux 22, Ernest Leitz Wetzlar GmbH, Germany) that was attached to a digital camera (AxioCam MRC5, Carl Zeiss Vision GmbH, Germany) for capturing images of pellets. Feret diameters, circularity (F_c), aspect ratio (AR), projected area and perimeter were directly derived by the image analysis software and by using appropriate formulas as described²⁴.

2.5 Particle morphology by scanning electron microscope

Morphology and surface texture of pellets (sieve fraction: 0.71-1.0mm) were inspected using a scanning electron microscopy (SEM) (Hitachi S3000N, Hitachi High Technologies America Inc., Pleasanton, CA). Pellets were placed on a 15mm double-sided carbon adhesive aluminium specimen stub (Agar Scientific, Essex, UK). The specimens were then coated with palladium and gold under argon atmosphere by a sputter coater (model SC7620, Quorum technologies, UK) with a processing current of 18-20mA for 2×10^5 s as described²⁵. The raw materials were also examined.

2.6 Flowability of pellets

Approximately 6g of pellets (sieve size: 0.71-1.0mm) were poured into a measuring cylinder without any vibration to determine the maximum bulk volume (V_b) of pellets. Volume readings after each 10 taps interval were recorded till the difference in tapped volume and the last volume reading was not changed by over 1ml. This is regarded as minimum bulk volume (V_t) of the pellets. In this study, around 80 taps were required to reach V_t . The bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) were calculated by dividing mass of the sample by V_b and V_t , respectively, for each sample. Carr's Compressibility Index (CI) and Hausner Ratio (HR) can be calculated according to the equations stated in British Pharmacopoeia (BP)²⁶ and presented below,

$$CI (\%) = [(\rho_{tapped} - \rho_{bulk}) / \rho_{tapped}] \times 100\%$$

$$HR = \rho_{tapped} / \rho_{bulk}$$

Flow properties of the samples could then be described based on the scale of flowability as described²⁶. The same procedure was applied to raw powder materials. The experiment was conducted twice for each specimen.

2.7 Apparent density

The apparent density of pellets (sieve fraction: 0.71-1.0mm) was measured in duplicate using a helium multi-pycnometer (Quantachrome Instruments, Boynton Beach, USA). Initially, the equipment was calibrated using standard steel balls to determine the reference volume (V_R) and the total volume of the system (V_C). Then, a known weight of pellets was placed in a microcell-sample holder. The system was connected to helium gas that functioned in removing any gas adsorbed on the pellet surface. The pressure of a fixed amount of gas in the reference (P_1) and pressure of a fixed amount of gas in sample cell (P_2) were recorded. The apparent volume of pellet (V_p) was determined using the equation as shown below,

$$V_p = V_C - V_R ((P_1/P_2) - 1)$$

The apparent density of pellets was calculated by dividing the sample mass by V_p value. The density measurements were repeated for the raw ingredients.

2.8 Pellet tensile strength

The mechanical testing instrument (CT-5 Engineering System, Nottingham, UK) was fitted with a 5kN load cell and the speed of the upper platen was set at 1mm.min⁻¹. The force that was used to break each pellet was obtained. Twenty randomly selected pellets (sieve size: 0.71-1.0mm) were used.

2.9 Calibration curve for indometacin

Indometacin powder was dissolved in phosphate buffer solution pH 7.2 to prepare a 500 μ g.mL⁻¹ stock solution. The stock solution was diluted with the same buffer to prepare calibration solutions ranging from 5 to 75 μ g.ml⁻¹. The drug absorbance values

were determined at 320nm using a UV spectrophotometer (CamSpec, UK). A good linearity was obtained with $R^2=0.9949$. The calibration equation was, absorbance = $0.0195 \times \text{Concentration } (\mu\text{g.ml}^{-1})$ and was used for further analysis.

2.10 Drug content determination and *In vitro* release profile and

For drug content uniformity test, 100mg of pellets were crushed and drug particles were dissolved in phosphate buffer pH 7.2. The samples were then diluted to a target concentration of $50\mu\text{g.ml}^{-1}$ before UV monitoring. Triplicate for each batch was used. Dissolution study of drug loaded pellets was performed using the BP dissolution Apparatus II (Erweka® GmbH, Germany) and in accordance to the conditions described in British Pharmacopoeia²⁷. IND loaded pellets (equal to 75mg of drug) were placed in each dissolution vessel containing 900ml phosphate buffer pH 7.2, maintained at 37°C. The paddles were rotated at 50rpm. Ten microliters of samples were withdrawn at the intervals of 10, 20, 30, 40, 50, 60, 120, 180, 240, 300, 360, 420 and 480 minutes. Following each withdrawal, a 10ml of buffer solution was immediately replaced. The drug absorbance values of each sample were determined at 320nm using UV-visible spectrophotometer (CamSpec, UK). The experiment was performed in triplicate.

2.11 Statistical analysis

Statistical analysis was performed using SPSS software (version 23.0, SPSS Inc. Chicago, USA). Data were compared by using one-way ANOVA where applicable and followed by a post hoc test. A p-value of less than 0.05 was considered as significant.

3. RESULTS AND DISCUSSIONS

Extrudates were found to be typically long and cylindrical in appearance with smooth surfaces. The overall yield after extrusion was roughly 70% for batches with and without drug. Hence, the lost during extrusion step was the highest. This was partly due to the fact that materials stuck to the extrusion rotor as well as lost due to sample transfer.

3.1 Pellet size and shape

In our preliminary work, when water or when 80% and over of water in the mixed solvent system was used, extrudates could not be rounded and the yields of the pellets were low for formulations consisting of HPMC, Prosolv® SMCC 90 and DCP (data not presented). Reasonable pellet yields were obtained when IPA content in the liquid binder was further increased. The modal class of these pellets was mainly found in 0.71-1.0mm as the die hole for extruder screen is 1.0mm. Despite using a mixed solvent system, the optimal ratio of liquid binder to spheronization aid was found to be similar to those produced with water for Prosolv® SMCC 50 based pellets⁷.

For blank pellets, except for A1 and A2, all other pellets recorded <10% fine or coarse

fractions indicating the amount of liquid binder used was at appropriate level. The typical IQR ranged 0.18-0.25mm and this is similar to our previous studies^{7, 25}. Based on Table 1, except for A1, A2-A4 where decreasing proportion of water was employed (3/7, 3.5/6.5, 4/6 of IPA/water), median diameters of the pellets were only increased slightly indicating there was a modest pellet growth while there was an increase in the yields. This has showed that mixed solvent eased the production of pellets. Apart from particle growth to the expected size, shape is an important characteristic for pellet. An ideal shape of pellet should have an aspect ratio <1.2 and a circularity (Fc) value close to 1.0²⁸. The pellets adhered to these criteria when mixed solvent system was kept at 3.5/6.5 of IPA/water (Figure 1). Hence, for the remaining work, this ratio was used. By keeping HPMC 80-120cp content at 10%, there is no remarkable difference in terms of median diameters and aspect ratios among the pellets of A5, A6 and A3 with a 2.5% increment of DCP from 5 to 10%. While comparing the two grades of silicified MCC, B1 and B2 that consisted of 85% and 80% Prosolv[®] SMCC 50 at 10% DCP, they had smaller aspect ratio values than those made with Prosolv[®] SMCC 90 of the similar compositions, i.e. A3 and A7, where the aspect ratio values were 1.1-1.12 and 1.14-1.16, respectively. Thus, despite its larger particle size, Prosolv[®] SMCC 90 has limited effect on shape of the pellet when manufactured at the right conditions. Pellet roundness reduced with an increase in HPMC viscosity²⁹. Pellets at 80% Prosolv[®] SMCC 90, 10% DCP were compared for HPMC viscosity effect. C1, which was produced with HPMC 12-18cp (at 10%), possessed a larger size than A3 due to use of slightly higher level of liquid binder. It has an aspect ratio of 1.12. When HPMC 12-18cp content was increased to 20% by keeping DCP level constant, aspect ratio increased to 1.2 without growth of pellet size (D_{50} value of C2=0.87mm). This showed that a lower percentage of HPMC and higher percentage of silicified MCC produced rounder pellets. Increasing HPMC level made it harder to round off the extrudates regardless of the HPMC viscosity. For drug loaded pellets, decreasing Prosolv[®] SMCC 90 content and with a small reduction in the amount of liquid binder as in D2 had also produced smaller median diameter corresponding to those without drug. Despite applying the maximum spheronization speed and extending residence time beyond 10 minutes, we observed no further size growth. HPMC was not pre-dissolved as part of the liquid binder instead it was added directly as part of pellet matrix. Unlike MCC that acts like a sponge, HPMC particles swell and dissolve gradually in the liquid binder and increase tackiness of extrudates making them harder to spheronize and for materials to transfer. In summary, whether the extrudates can be rounded off directly, or broken down initially and then re-grow to the required size and shape depend on formulation compositions, nature of liquid binder and process conditions. Compaction of wet mass into extrudates is

strongly influenced by the water sorption on MCC. Structural re-arrangement of HPMC on exposure to water is anticipated and this leads to viscous gel formation that changes rheological property of the wet mass. Moreover, wetting of whole powder blend can be retarded and less even fluid distribution occurs as HPMC gel layer acts as retardant for fluid penetration. This has led to formation of lumpy agglomerates that is difficult to handle³⁰. Isopropanol has no such effect and suppressed HPMC hydration. Thus the presence of IPA can improve consistency of the wet mass containing HPMC. Sphericity of pellets was improved as IPA ratio is increased in liquid binder (Figure 1). Water is still needed for many reasons including as a plasticizer and a lubricant. It also maintains cohesive strength for shaping of extrudates into pellets²⁵.

3.2 Powder and pellet flow property

Cohesiveness of powder can be indicated by Hausner ratio (HR) where values between 1.25 and 1.4 are considered having an intermediate flow with some cohesive properties. Meanwhile, Carr's compressibility index (CI) is a direct measure of potential powder arch or bridge strength. CI has been related to material flow and is dependent on the measured bulk and tapped density values³¹. Powders are typical free flowing when their sizes are larger than 250 μ m and become cohesive and experience flow issue when the sizes fall below 100 μ m³². Based on scale of flowability²⁶, DCP, HPMC 80-120cp and IND possessed poor flow (Figure 1). This is because these powders are small in size and have a relatively high surface area to volume ratio and inter-particulate forces are dominating leading to poor flow. SEM images confirmed that powder excipients and IND were fine and had irregular shapes with rough surfaces (Figures 2a-f). CI and HR values of the pellets were less than 10% and 1.1, respectively, regardless of type of spheronization aids. There was little correlation between aspect ratio and CI or HR value of Prosolv[®] SMCC 90 based pellets ($R^2=0.23-0.25$). Thus size enlargement is the key factor that the pellets having better flow than the respective powders.

3.3 Apparent density by helium pycnometer

Size and shape of raw materials as well as packing of the materials upon processing affect density and hence porosity of pellets. Based on results above, A1, which was the least spherical in shape and with the largest in median diameter has the highest apparent density compared to those pellets made with lower water ratios in liquid binder (A2-A4, Figure 3). This is unexpected because the least spherical and larger size tends to be more porous and thus having a lower density. As the liquid binder was made of 80% water for A1, a greater extent of HPMC gelling was anticipated to strengthen particle binding. The apparent densities of other pellets were similar ranging 1.51-1.59g.cm⁻³ indicating the compaction of the pellets were of similar degrees as they were processed using the same conditions. The density of pellets loaded with drug also fell

within the lower end of this range as indometacin has a smaller true density than DCP. C2 made with 20% HPMC 12-18cp exhibited the lowest apparent density, partly due to the fact that the extrudates could not be rounded off and it was made of the highest quantity of HPMC that possessed lower true density.

3.4 Breaking load of pellet

The pellets produced using silicified MCC with addition of HPMC had good mechanical strength (Figure 3). A1 required a higher breaking load than A2-A4, as it was prepared with a binder with a higher ratio of water where a larger number of liquid bridges formed that enabled more particles interacted after process manipulation¹⁸. Higher HPMC content led to mechanically stronger pellets in their dried forms supporting previous observations¹⁷. Pellets that were made of higher silicified MCC but lower HPMC content (D1, A7 and B1) exhibited lowered breaking loads. Increasing the amount of HPMC led to mechanically stronger pellets in their dried forms due to creation of gel structure that give better bonding amongst other powder particles (Figure 3). For drug loaded pellet, unlike D1 where pellets were completely crushed under applied force, this was not seen with D2, which meant the pellets were more rigid in nature. The breaking loads of A3 was higher than C1 as a higher viscosity HPMC 80-120cp was used that could link with creation of thicker gel layers that form around particles. By increasing the low viscosity grade HPMC 12-18cp to 20%, the breaking load increased as seen in C2. These results support the idea that HPMC viscosity and composition are the key factors governing crushing strength of pellet. Based on One-way ANOVA, only pellets with mean breaking load values <7N were found to be significantly smaller than A1 ($p < 0.05$). It has been previously showed that apparent pellet density is linked to its mechanical strength³³. Figure 4 showed the breaking loads of pellets are related to the apparent density of pellets while the effect of size was less prominent based on the evaluation using D_{50} values. As size increases while density remains similar, surface area to volume ratio will be smaller. Thus interactions amongst particles reduced and these pellets will require smaller force to be deformed. It was not apparent in our case as R^2 was small because D_{50} of pellets were similar ranging 0.82-0.97mm.

3.5 Drug content uniformity test and *In vitro* release study

Pellets conformed to the BP drug content uniformity (target: 90-110%). The drug content for D1 was 96.4- 98.4% and D2 was 92.6-95.4%. The pellets exhibited modified release profiles where drug release was faster during the first few hours and then became more gradual (Figure 5). Indometacin has a pK_a value of 4.5³⁴, it ionizes in the medium with higher pH, and high fraction of ionized species is expected at pH 7.2. Drug release was retarded as IND particles were packed within the pellet matrix. Only when the matrix is hydrated, drug dissolution occurs. Dissolved drug molecules are released

from the pellets by various mechanisms, including diffusion via the swollen matrix layer and/or via matrix erosion due to weakened gel layer. A study has shown that there were immediate and steady drug release for MCC and HPMC based tablets, respectively³⁵. This was because hydration of MCC differs from HPMC. Water molecules were trapped within the MCC sponge to induce local swelling of matrix³⁶ meanwhile a regular hydration was seen in Methocel E15LV granules as fully amorphous HPMC allowed greater water mobility to occur than MCC³⁵. At the end of 8th hour, D1 and D2 gave approximately 55% and 90% drug release, respectively. Dissolution profiles of the pellets were compared after calculating the similarity index (F2) value, and the dissolution profiles differ with the F2 value of 28.3%³⁷. The pellet dissolution profiles were further analyzed for the best fitted kinetic models³⁸. From our analysis, D1 is best described with Higuchi model ($R^2=0.9966$) while D2 adhered best to Kosmeyer-Peppas (KS) model ($R^2=0.9915$). However D1 also fitted to KS model ($R^2=0.9922$). The diffusional exponent (n) values for D1 and D2 based on based on KS model were 0.65 and 0.86, respectively, indicated a non-Fickian or anomalous transport ($0.45 < n < 0.89$) for the drug release mechanism³⁸. As expected with our pellets, applying low viscosity grade HPMC produces gel with less resistance to mechanical stresses that tends to dissolve faster and erodes more rapidly also we limited the HPMC content up to 10%³⁹. A faster dissolution rate of D2 can be further explained as higher HPMC content increased wettability of insoluble drugs or matrix that has resulted in higher and faster medium uptake into the pellets due to formation of more pores or water channels²¹. Larger pores were seen on the surface of pellets after dissolution test (Figures 2i-j) compared to those before the test (Figures 2g-h). This indicated that drug release and matrix erosion had occurred. Meanwhile, signs of fragmentation were observed in D2 supporting that more drug was released as the gel formed could not be held together.

4. CONCLUSIONS

Water is normally used as the liquid binder in extrusion and spheronization. However, with addition of HPMC to the pellet, it is not ideal. Instead, combination of organic solvent with water is successful to act as liquid binder for hydrophilic matrix component. The optimal water to IPA ratio that can be used to produce pellets is 6.5 to 3.5 without compromising key pellet properties including size distribution, shape and mechanical property. Prosolv[®] SMCC 90 based pellets with low viscosity HPMC grades have good flow property despite higher aspect ratios, and high yield is obtained. Their mechanical strengths were comparable to Prosolv[®] SMCC 50 based pellets. The presence of low quantity of HPMC 80-120cp up to 10% altered the release of indometacin from the

pellets. More HPMC and less silicified MCC increased the overall drug release. This is based on faster wetting of compact with limited gel formation. In summary, we produced indometacin loaded pellets using HPMC as modifier and Prosolv® SMCC 90 as key spheronization aid while employing mixed solvent consisting IPA/water that had enabled the manufacture of modified release pellet formulation.

Declaration of Interest

All the authors of this manuscript report no conflict of interest.

5. REFERENCES

1. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment--a review. *Int J Pharm* 2014; 473: 64-72.
2. Chamsai B, Sriamornsak P. Novel disintegrating microcrystalline cellulose pellets with improved drug dissolution performance. *Powder Technol*; 2013, 233: 278-285.
3. Rowe RC, Sheskey PJ, Quinn ME. Cellulose microcrystalline. In: *Handbook of Pharmaceutical Excipients*, 6th ed., Pharmaceutical Press, 2009; 129–133.
4. JRS Pharma. PROSOLV® SMCC: Silicified Microcrystalline Cellulose. Available at <http://www.jrspharma.com/pharma-wAssets/docs/brochures/PROSOLV-SMCC.pdf> [Accessed 12th September 2018]
5. Lahdenpaa E, Antikainen O, Yliruusi J. Direct compression with silicified and nonsilicified microcrystalline cellulose: Study of some properties of powders and tablets. *STP Pharm Sci*, 2001; 11: 129-135.
6. Luukkonen P, Newton JM, Podczeck F, Yliruusi J. Use of a capillary rheometer to evaluate the rheological properties of microcrystalline cellulose and silicified microcrystalline cellulose wet masses. *Int. J Pharm*, 2001; 216(1-2): 147-157.
7. Mustafa O, Chaw CS. Silicified microcrystalline cellulose based pellets and their physicochemical properties. *J Appl Polym Sci*, 2016; 133: 43829.
8. Sarkar S, Ang BH, Liew CV. Influence of starting material particle Size on pellet surface roughness. *AAPS PharmSciTech*, 2014; 15(1): 131–139
9. Arca HC, Mosquera-Giraldo LI, Bi V, Xu D, Taylor LS, Edgar KJ. Pharmaceutical applications of cellulose ethers and cellulose ether esters. *Biomacromolecules*, 2018, 9; 19(7): 2351-2376.
10. Zhang J, Yang W, Vo A, Feng X, Ye X, Kim D, Repka M. Hydroxypropyl methylcellulose-based controlled release dosage by melt extrusion and 3D printing:

Structure and drug release correlation. *Carbohydr Polym*, 2017; 177: 49-57.

11. Katzhendler I, Mäder K, Friedman M. Structure and hydration properties of hydroxypropyl methylcellulose matrices containing naproxen and naproxen sodium. *Int J Pharm*, 2000; 200(2): 161-179.
12. Mitchell S, Reynolds T, Dasbach T. A compaction process to enhance dissolution of poorly water-soluble drugs using hydroxypropyl methylcellulose. *Int J Pharm*, 2003; 250(1): 3-11.
13. Sigma-Aldrich. Hydroxypropylmethylcellulose.
<https://www.sigmaaldrich.com/catalog/product/sigma/h9262?lang=en®ion=GB> (accessed 12th September 2018)
14. Dow Chemical Company. METHOCEL cellulose ethers in aqueous systems for tablet coating. <https://www.dow.com/scripts/litorder.asp?filepath=/198-00755.pdf> (assessed 12th September 2018)
15. Mascia S, Seiler C, Fitzpatrick S, Wilson D. Extrusion–spheronisation of microcrystalline cellulose pastes using a non-aqueous liquid binder. *Int J Pharm*, 2010; 389(1-2): 1-9.
16. Chatlapalli R, Rohera B. Physical characterization of HPMC and HEC and investigation of their use as pelletization aids. *Int J Pharm*, 1998; 161(2): 179-193.
17. Zoubaria G, Ali R, Dashevskiya, A. Water-soluble and -insoluble polymers as binders for pellet preparation by extrusion/spheronization. *J Drug Deliv Sci Technol*, 49, 1-5.
18. Sarkar S, Liew C. Moistening liquid-dependent de-aggregation of microcrystalline cellulose and its impact on pellet formation by extrusion–spheronization. *AAPS PharmSciTech*, 2014;15 (3): 753-761.
19. Schröder M, Kleinebudde P, Structure of Disintegrating Pellets with Regard to Fractal Geometry. *Pharm Res*, 1995; 12(11): 1694-1700.
20. Dreu R, Širca J, Pintye-Hodi K, Burjan T, Planinšek O, Srčić S. Physicochemical properties of granulating liquids and their influence on microcrystalline cellulose pellets obtained by extrusion-spheronisation technology. *Int J Pharm*, 2005; 291(1-2): 99-111.
21. Mahrous, GM, Ibarhim MA, El-Badry M, Al-Anazi FK. Indomethacin sustained release pellets prepared by extrusion-spheronization. *J Drug Del Sci Tech*, 2010; 20 (2): 119-125.
22. British Pharmacopoeia Commission. Indometacin. *British Pharmacopoeia*, volume I. London: TSO; 2018.
23. Rowe, RC, Sheskey PJ, Quinn ME. Dibasic calcium phosphate dehydrate. In: *Handbook of Pharmaceutical Excipients*, 6th ed., Pharmaceutical Press, 2009; 96-

24. Podczeczek F, Rahman SR, Newton JM. Evaluation of a standardised procedure to assess the shape of pellets using image analysis. *Int J Pharm* 1999; 192: 123–38.
25. Puah S, Yap H, Chaw CS. Production and characterization of pellets using Avicel CL611 as spheronization aid. *Drug Dev Ind Pharm*. 2014; 40(3): 418-424.
26. British Pharmacopoeia Commission. Powder flow. British Pharmacopoeia, Appendix XVII N, Volume V. London: TSO; 2018.
27. British Pharmacopoeia Commission. Indometacin Capsule. British Pharmacopoeia, Volume III, London: TSO; 2018.
28. Olson E. Particle shape Factors and Their Use in Image Analysis- Part 1: Theory. 2011; *GXP*, 15(3).
29. Garekani HA, Nokhodchi A, Rayeni MA, Sadeghi F. Preparation and characterization and release properties of Eudragit RS based ibuprofen pellets prepared by extrusion spheronization: effect of binder type and concentration. *Drug Dev Ind Pharm*, 2013; 39(8): 1238-46.
30. Darunkaisorn W, Mahadlek J, Phaechamud T. HPMC matrix granule formation: Selection of Suitable Granulating Fluid. *Thai Pharm Health Sci J*, 2009; 4(1): 29-45
31. Shah RB, Tawakkul MA, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. *AAPS PharmSciTech*, 2008; 9(1): 250–258.
32. Liu L, Marziano I, Bentham A, Litster J, White ET, Howes T. Effect of particle properties on the flowability of ibuprofen powders. *Int J Pharm*, 2008; 362(1-2): 109-117.
33. Sousa J, Sousa A, Podczeczek F, Newton JM. Factors influencing the physical characteristics of pellets obtained by extrusion-spheronization. *Int J Pharm*, 2002; 232(1-2): 91-106.
34. O'Neil, M.J. (ed.). *The Merck Index - An encyclopedia of chemicals, drugs, and biologicals*. Cambridge, UK: Royal Society of Chemistry, 2013, pp. 922.
35. Chambin O, Champion D, Debray C, Rochat-Gonthier M, Le Meste M, Pourcelot Y. Effects of different cellulose derivatives on drug release mechanism studied at a preformulation stage. *J Control Release*, 2004; 95(1): 101-108.
36. Lustig-Gustafsson C, Kaur Johal H, Podczeczek F, Newton J. The influence of water content and drug solubility on the formulation of pellets by extrusion and spheronisation. *Eur J Pharm Sci*, 1999; 8(2): 147-152.
37. Duan JZ, Riviere K, Marroum P. In vivo bioequivalence and in vitro similarity factor (f_2) for dissolution profile comparisons of extended release formulations: how and when do they match? *Pharm Res*, 2011; 28(5): 1144-56.

38. Groves E, Chaw CS. Incorporation of calcium salts into xanthan gum matrices: hydration, erosion and drug release characteristics. *Drug Dev Ind Pharm.* 2015; 41(10): 1608-16.
39. Dow Chemical Company. Using METHOCEL Cellulose Ethers for Controlled Release of Drugs in Hydrophilic Matrix Systems. <https://www.colorcon.com/products-formulation/all-products/download/677/2063/34?method=view> (assessed 12th September 2018)

List of table

Table 1 Formulation compositions, Size distribution and yield values of the pellets.

Table 1 Formulation compositions, size distribution and yield values of the pellets.

Batch ID	DPC or IND (%)	Silicified MCC (%)	HPMC (%)	Liquid binder (%w/w) ^c	Water: IPA	D ₅₀ (mm)	IQR (mm)	Yield (%)	Fine fraction (%)	Coarse fraction (%)
A1	10	80	10	80.1	8:2	0.97	0.42	81.69	0.00	18.31
A2	10	80	10	65.2	7:3	0.78	0.24	89.43	10.57	0.00
A3	10	80	10	75.4	6.5:3.5	0.82	0.18	95.60	4.84	0.00
A4	10	80	10	71.9	6:4	0.85	0.18	94.98	5.02	0.00
A5	5	85	10	81.3	6.5:3.5	0.85	0.18	97.76	2.24	0.00
A6	7.5	82.5	10	78.2	6.5:3.5	0.85	0.18	99.23	0.77	0.00
A7	10	85	5	81.9	6.5:3.5	0.89	0.18	99.38	0.62	0.00
B1	10	85 ^a	5	82.3	6.5:3.5	0.86	0.17	98.65	1.35	0.00
B2	10	80 ^a	10	79.1	6.5:3.5	1.01	0.25	96.93	3.07	0.00
C1	10	80	10 ^b	79.8	6.5:3.5	0.97	0.20	99.03	0.00	0.97
C2	10	70	20 ^b	70.6	6.5:3.5	0.87	0.18	98.70	0.47	0.80
D1	10 ^d	85	5	80.1	6.5:3.5	1.01	0.25	97.64	2.35	0.00
D2	10 ^d	80	10	78.4	6.5:3.5	0.81	0.24	94.78	2.78	2.44

^a Indicates Prosolv[®] used was SMCC 50, and the remaining pellets used SMCC 90.

^b Indicates Methocel[™] E15 LV was used, the remaining pellets used HPMC 80-120 cp

^c Percentage of liquid binder was calculated based on total dried powder mass.

^d These formulations were loaded with IND rather than DCP.

List of figures

Figure 1 Flow properties and shape parameters of pellets and raw materials. The flow properties were Carr's compressibility index (CI, represented by line) and Hausner ratio (HR, grey bars) values and the shape parameters were aspect ratio (AR, white bars) and circularity (Fc, black bars) values. Bars and symbol on line represent mean values.

Figure 2 SEM images of raw materials and IND loaded pellets before and after dissolution tests at different resolutions. (a) HPMC 12-18cp, (b) HPMC 80-120cp, (c) DCP, (d) Prosolv[®] SMCC 50, (e) Prosolv[®] SMCC 90, (f) IND; (g1-3) D1 pellets before dissolution test; (h1-3) D2 pellets before dissolution test; (i1-3) D1 pellets after dissolution test; (j1-3) D2 pellets after dissolution test. Similar morphology was observed for blank pellets (images not inserted).

Figure 3 Density for raw materials and pellets as determined by pycnometer (solid bars) and breaking load values of pellets (open bars). Bars represent mean values.

Figure 4 Relationship between breaking loads and median diameters (D_{50}) or apparent density of pellets made with HPMC 80-120cp, Prosolv[®] SMCC 90 and DCP of various compositions (A1 –A7).

Figure 5 *In vitro* release profiles of IND loaded pellets.

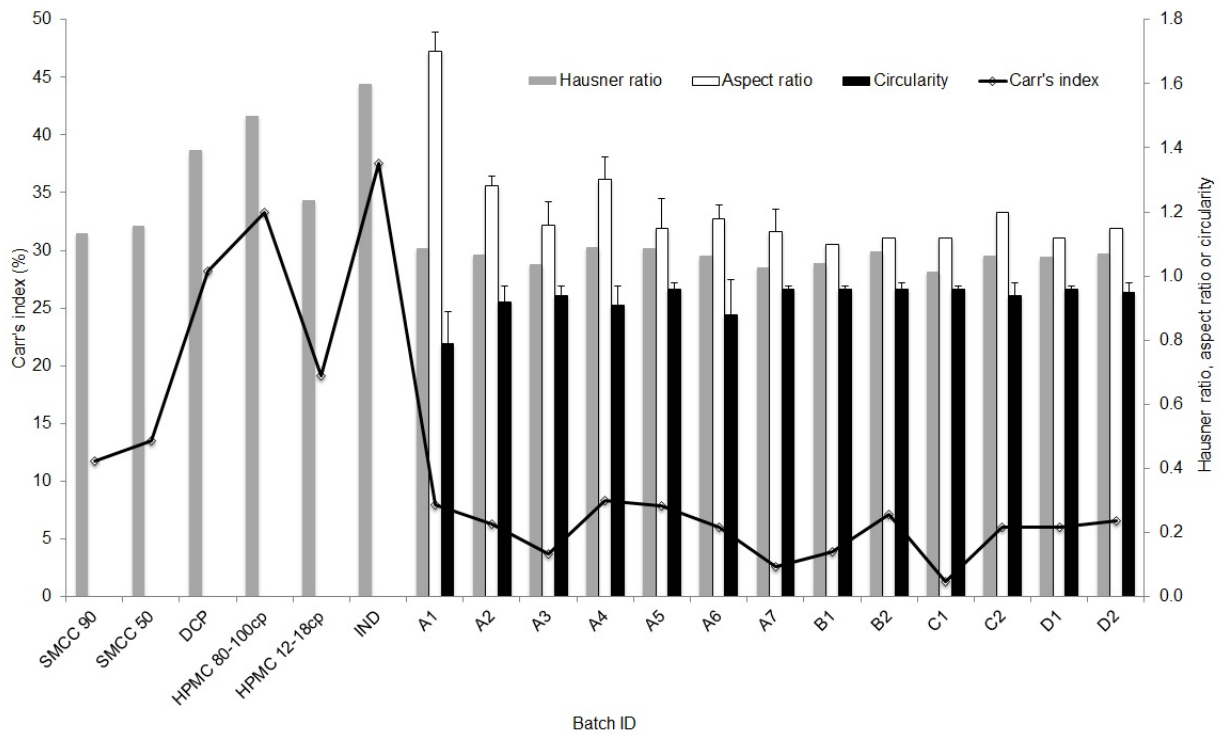


Figure 1 Flow properties and shape parameters of pellets and raw materials. The flow properties were Carr's compressibility index (CI, represented by line) and Hausner ratio (HR, grey bars) values and the shape parameters were aspect ratio (AR, white bars) and circularity (Fc, black bars) values. Bars and symbol on line represent mean values.

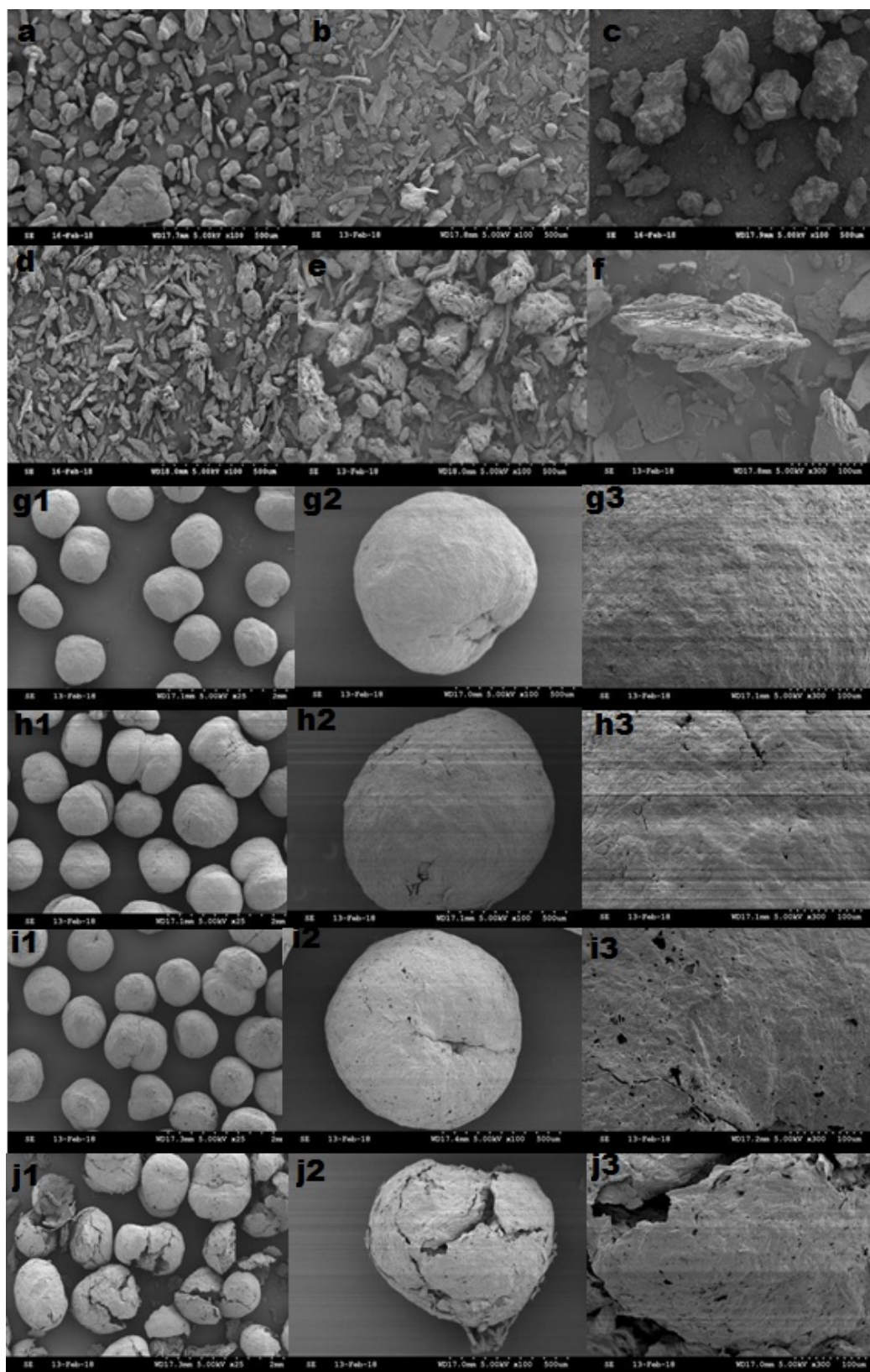


Figure 2 SEM images of raw materials and IND loaded pellets before and after dissolution tests at different resolutions. (a) HPMC 12-18cp, (b) HPMC 80-120cp, (c) DCP, (d) Prosolv® SMCC 50, (e) Prosolv® SMCC 90, (f) IND; (g1-3) D1 pellets before dissolution test; (h1-3) D2 pellets before dissolution test; (i1-3) D1 pellets after dissolution test; (j1-3) D2 pellets after dissolution test. Similar morphology was observed for blank pellets (images not inserted).

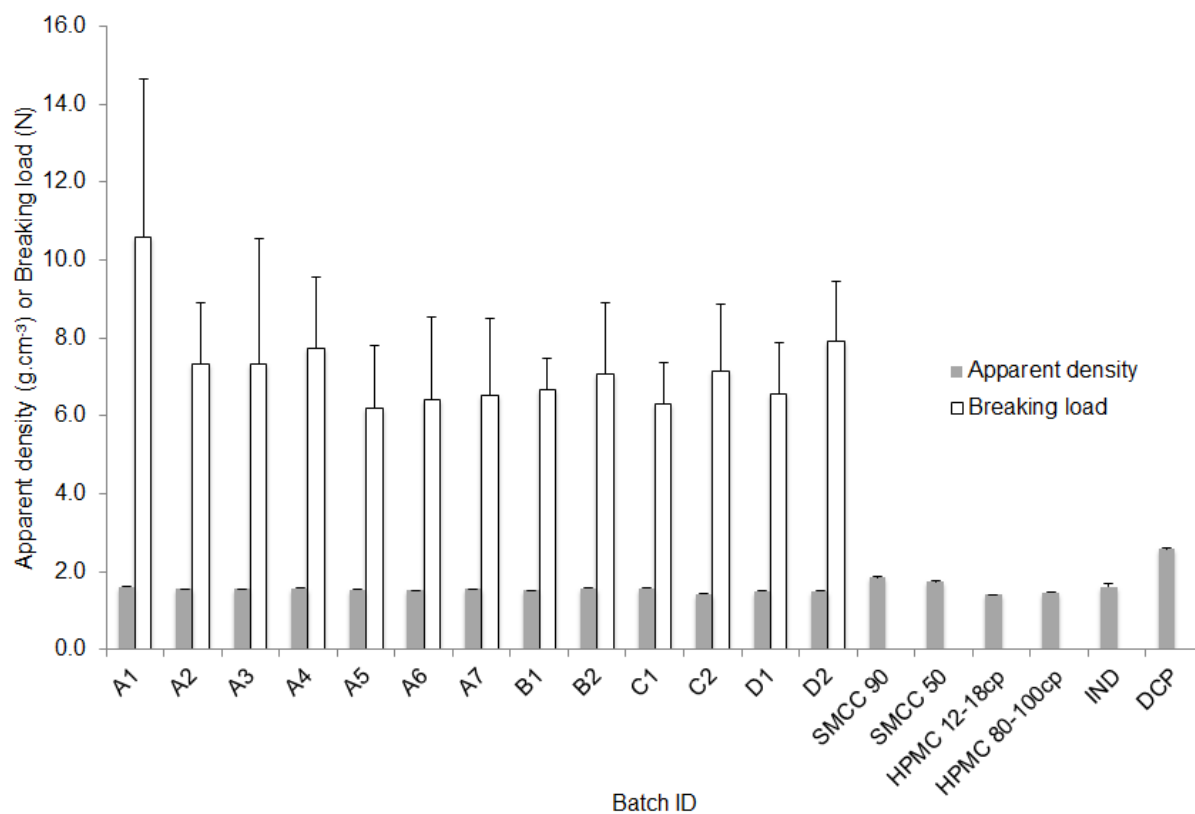


Figure 3 Density for raw materials and pellets as determined by pycnometer (solid bars) and breaking load values of pellets (open bars). Bars represent mean values.

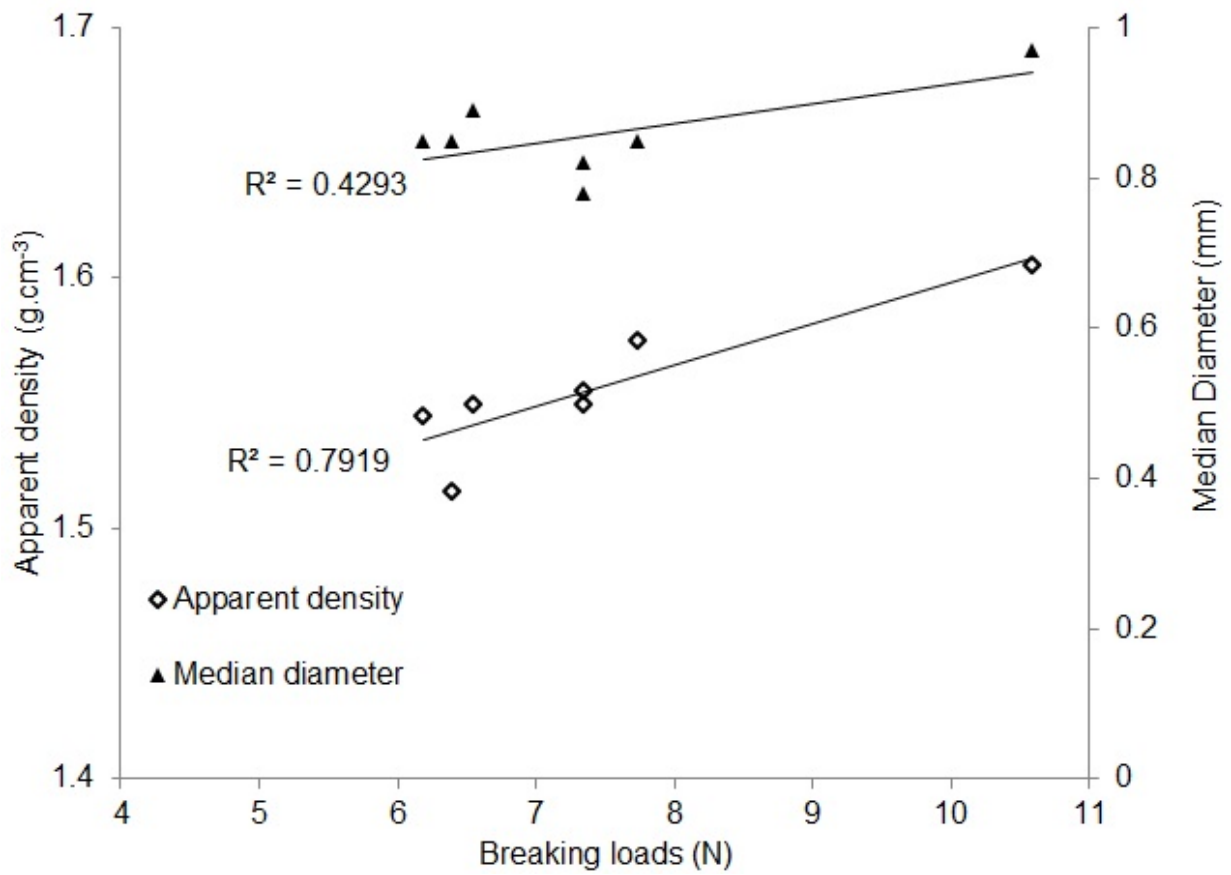


Figure 4 Relationship between breaking loads and median diameters (D_{50}) or apparent density of pellets made with HPMC 80-120cp, Prosolv[®] SMCC 90 and DCP of various compositions (A1 –A7).

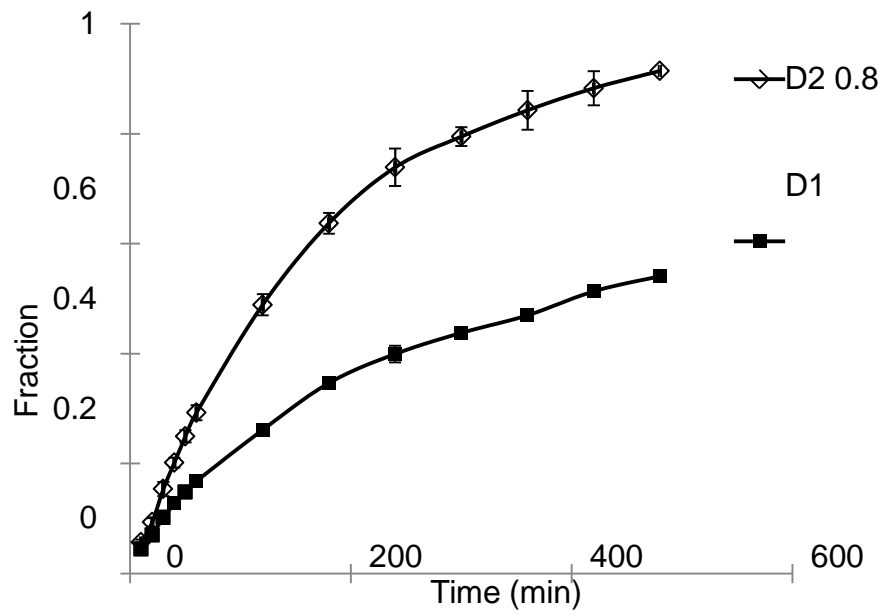


Figure 5 *In vitro* release profiles of IND loaded pellets.