

Original Article

COMPARATIVE EVALUATION OF THE RELEASE PROPERTIES OF VERAPAMIL HCL AND CARBAMAZEPINE FROM MICROCRYSTALLINE CELLULOSE II PELLETS

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ABSTRACT

Objective: To study microcrystalline cellulose II (MCCII) as new pelletization aid for a high and low solubility drugs such as verapamil. HCl and carbamazepine, respectively.

Methods: Approximately, 30 g of MCCII and drug mixtures were hydrated, passed through a # 20 mesh sieved and spheronized at a frequency of 6 Hz and residence time of 480 s. A microscopy analysis was used to evaluate the shape and size descriptors. Pellets properties such as compressibility, friability, density, flowability and product yield were also evaluated. Drug release properties were tested according to the USP specifications and compared to those of MCCII.

Results: The wetting level of the excipients depended on drug loading and drug solubility. Thus, a high drug loading (>50%) rendered pellets having a low yield, flowability and caused a detriment on size descriptors. Likewise, the regular morphology and strength of MCCII-based pellets was highly affected by increasing drug loads. Verapamil. HCl pellets were less friable and compressible and showed better flowability than carbamazepine pellets. Regardless of drug loading and drug solubility, MCCII-based pellets released more than 80% of verapamil. HCl within 10 min, whereas released more than 75% of carbamazepine within 15 min. Conversely, MCCII pellets had a satisfactory verapamil. HCl release, but ~30% carbamazepine release within 1h.

Conclusion: MCCII proved to be a better excipient than MCCII to yield beads having optimal pellet characteristics, and rendered an immediate release profile for verapamil. HCl and carbamazepine.

Keywords: Extrusion-spheronization, Microcrystalline cellulose II, Verapamil HCl, Carbamazepine

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INTRODUCTION

Pelletization is one of the most favourable technologies for manufacturing a multiparticulate drug delivery system. Thus, pellets are defined as agglomerates of granules or fine powders of bulk drugs and excipients [1]. They consist of free-flowing, spherical or semi-spherical particles, typically from about 0.5-2.0 mm and are usually coated and intended for oral administration [2]. Pellets exhibit advantages over tablets such as less irritation, and a lower risk of side effects due to dose dumping at the mucosa focus site, have a lower tendency of adhering to the esophagus, provide a good distribution and smoother drug absorption profile in the GI tract due to the less variable transit times. As a result, they render reproducible drug blood levels and leave the stomach rapidly regardless of the gastric emptying rate, feeding, or nutritional state of the patient [3].

Currently, microcrystalline cellulose I (MCCI) is the most widely used excipient for the manufacture of pellets by extrusion-spheronization. However, MCCI-based pellets containing low soluble drugs might show a tendency to have a prolonged drug release profile due to the lack of disintegration. Alternative substitutes of MCCI such as carrageenan, starch, glycerides, croscopolidone, chitosan, cyclodextrins and pectinic acid could lead to the formation of ionic charges, render an inadequate pellet shape, flexibility, and a low drug loading capacity, resulting in granules of insufficient mechanical strength and water holding capacity [4]. One promising alternative is the use of MCCII as a pelletization aid. This excipient was primary introduced as a new excipient for direct compression. It produces compacts having a rapid disintegration regardless of the compact porosity [5]. However, the study of the release properties of drugs commonly commercialized as tablets and having extreme solubilities from pellets made of MCCII is still unexplored. Therefore, the purpose of this study was to evaluate the pelletization features of MCCII as compared to the MCCI allomorph using verapamil. HCl

and carbamazepine as models for a high (BSC class I, 83 mg/ml) and low solubility (BSC class II, 17.7 mg/l) drugs, respectively.

Verapamil. HCl is used for the treatment of heart disease, especially that related with supraventricular tachyarrhythmias. It suffers from a first pass effect, has a short biological half-life (4-6 h), a low bioavailability and requires a high frequency of administration to maintain effective plasma levels. As a result, the incidence of side effects such as constipation, dizziness and headache is boosted leading to patient non-compliance and hence, therapeutic ineffectiveness [6]. On the other hand, carbamazepine is used for the treatment of seizures and convulsions. It stabilizes the neuron membranes and reduces the excitatory pulses. However, it exhibits a poor GI absorption upon oral administration leading to a variable therapeutical effect [7].

MATERIALS AND METHODS

Materials

Verapamil. HCl (lot YR3110) was donated from Ecar Laboratories. Avicel PH102 (lot P205815624) was purchased from FMC Biopolymers. Concentrated hydrochloric acid (37%, lot 2612KLHV) was purchased from Mallinckrodt Specialty Chemicals Co. Sodium lauryl sulfate (lot 98488) was obtained from fisher scientific (Fair lawn, NJ)

Methods

Preparation of verapamil. HCl (VH) and carbamazepine (CBZ) pellets

MCCII was obtained from cotton linters as reported previously [4]. Briefly, mixtures having ~30g of MCCII and the respective drug were prepared at the 90:10, 75:25, 50:50 and 25:75 drug: excipient ratio using a V-blender (Riddhi Pharma Machinery, Gulabnagar, India) for 10 min. Subsequently, distilled water was sprayed and mixed to get a wet mass and passed through a #20 mesh sieve (841 µm size) with

a force of $\sim 11.2 \text{ N/cm}^2$ measured with a load cell (LCGD-10K, Omega Engineering, Inc., Stamford, CT). The extruded thus obtained was put in the spheronizer chamber (Model 1LA70-4YA60, Siemens) and subjected to spheronization at the previously optimized conditions of 6 Hz and 480s. The resulting beads were then oven-dried at 60°C until the moisture content was less than 10%. Subsequently, beads were fractionated and particles with diameters larger than $250 \mu\text{m}$ were only utilized.

Pellet properties

The moisture content was determined using $\sim 1 \text{ g}$ of the sample on an infrared moisture balance (Scout Pro, OHAUS Corp., Parsippany, NJ) at 100°C for 10 min (Scout Pro, OHAUS Corp., Parsippany, NJ).

Flow rate was determined using $\sim 15 \text{ g}$ of sample passed through a glass funnel with a neck diameter of 13 mm and subsequently, the measurement of the flow time was taken. The ratio between mass and the respective time was taken as the flow rate.

Friability measures the pellet tendency to flake off during handling or transportation. This test was performed on $\sim 6.5 \text{ g}$ of the sample previously retained on a # 60 mesh. A friabilator (FAB-25 1,351,130, Logan) operated at 25 rpm for 4 min was employed. At the end of the test only the fraction retained on the # 60 mesh sieve was quantified.

Bulk density (ρ_{bulk}) was obtained directly from the ratio of $\sim 3 \text{ g}$ powder and its volume measured in a 10 ml graduate cylinder. Tap density (ρ_{tap}) was determined using an Autotap[®] density analyzer (AT2, Quantachrome Instruments, Boynton Beach) measuring the volume after 300 taps. Volume data for each cycle were fitted to the Kawakita compressibility model.

Shape and size descriptors

The morphology analysis and the particle size distribution were obtained by microscopy analysis. Optical micro pictures containing at least 650 particles were taken using an optical stereoscope (BM 180P, Boeco, Hamburg, Germany) at a 50x magnification coupled with a Fuji digital camera (FinePix S9000, Fujifilm, Tokio, Japan). The digital analysis of the micro pictures was done using the ImageJ software (v. 1.46r, NIH, Bethesda, MD). Particle size was obtained directly from the lognormal plots of the resulting distributions. The area perimeter and size were taken as size descriptors, whereas circularity, aspect ratio and roundness were taken as shape descriptors.

Verapamil HCl release studies

An amount of pellets containing $\sim 40 \text{ mg}$ of drug was tested in a type II dissolution apparatus (DT6-K, Erweka GmbH, Milford, CT). The test was conducted at 50 rpm in 900 ml of simulated gastric fluid (0.01 N HCl) for 30 min according to the USP specifications. Five-milliliter aliquots were withdrawn periodically and immediately replaced by a fresh dissolution medium. Aliquots were then filtrated through a $0.45 \mu\text{m}$ filter and measured directly. Samples were then analyzed by UV/VIS spectroscopy (HACH DR500, HACH Company, Loveland, CO) at 278 nm. The drug concentration was obtained by interpolation from a calibration curve built using 5, 14, 23, 46 and $92 \mu\text{g/ml}$ concentrations.

Carbamazepine release studies

An amount of pellets containing $\sim 100 \text{ mg}$ of drug was tested in a type 2 dissolution apparatus at 37°C and 75 rpm for 1h. 900 ml of distilled water containing 1% sodium lauryl sulfate was employed as a dissolution medium. The drug concentration was obtained by interpolation from a calibration curve built using 2, 4, 6, 10, 14 and $18 \mu\text{g/ml}$ concentrations using a UV/VIS spectrophotometer. Aliquots were then filtrated through a $0.45 \mu\text{m}$ filter and diluted using a dilution factor of 1:10. The absorbance readings were conducted at 288 nm. The uniformity content was determined on an amount of pellets containing $\sim 40 \text{ mg}$ and 100 mg of VH and CBZ, respectively. The uniformity content of both drugs within the pellets was determined on three different samples and analyzed for drug content.

Drug release models

The Weibull model with two parameters was employed to fit the fraction of drug released:

$$F = 1 - e^{-\left(\frac{t}{a}\right)^b} \dots\dots\dots (1)$$

Where, a and b correspond to the time scale dependence and dissolution shape profile, respectively. If b is $1, >1$ or <1 the profile is exponential, sigmoidal and steeply increasing, respectively. The Statgraphic software (vs. 4, StatPoint, Inc, USA) was used for the non-linear fitting employing the least square method.

RESULTS AND DISCUSSION

Pellet properties

Due to the high affinity of MCCII for water molecules, it functions as a "molecular sponge" retaining a high percentage of water conferring a degree of plasticity. Therefore, at low drug levels during extrusion, the wet mass was compressed until water was squeezed out and lubricated the particles. The volume of the extrudate expanded becoming less plastic, and thus, it was easily chopped and rounded into short lengths due to the friction and collision forces in the spheronizer plate. Conversely, as the level of drug in the MCCII mixture increased, this plasticity was lost and a higher level of water was required to award the adequate plasticity required for extrusion (table 1). In fact, this wettability was reduced to approximately one-third with respect to the pure MCCII. As a result, the amount of water required for the pelletization process was inversely related to the drug content. Therefore, pellets having a high drug load required less moistness and formed a tacky wet mass resulting in the formation of less spherical particles having a small size.

Since VH is a water-soluble drug, slightly smaller amounts of water were needed for pelletization than those required for CBZ. This was explained by the high capillarity phenomena inside the pellets. These capillary forces could lead to an excess of water at the surface of the pellets during spheronization. Due to the moistness at their surface, these pellets tend to stick together and densified into large agglomerates. Thus, VH dissolved in water slightly increasing the volume of the liquid phase with respect to the solid mass leading to an overwetting of the system. For this reason, less water was required to form a plastic mass to pass through the screen as the VH load increased. Conversely, water showed a poor wettability on CBZ pellets due to its poor solubility.

Results indicate that the capability of the powder mixture to bind moisture was critical for the spheronization process. Thus, water molecules formed hydrogen bonds with the hydroxyl groups of MCCII enhancing particle contacts points, interparticle cohesion, and stimulating wall slip and as a result, it eased some of the stresses generated during the agglomeration and spheronization processes. Thus, it was crucial to conduct the wetting and agglomeration processes rapidly (within 30 min) so water molecules do not evaporate or move around the mass particulate network leaving regions of the powder mass dewatered [8]. The levels of water required were highly associated to the screen size and geometry, and the drug packing characteristics and thus, the compressibility of pellets increased with increasing water levels for CBZ, whereas it remained unchanged for VH. In fact, the same material would require higher levels of water if a larger screen size is used [9]. On the other hand, the wet pellets need to be dried at a moderate temperature ($\leq 60^\circ \text{C}$) to prevent drug degradation. Further, during the drying process pellets shrank by capillary pressure due to the high surface tension of water as reported for MCCII [10]. Likewise, the final moisture content was below 10% which is acceptable for cellulosic materials.

Table 1 shows the resulting pellet properties for the two types of drugs. Regardless of the drug used product yield was around 20% and decreased drastically at drug levels $\geq 75\%$. This low yield was attributed to the loss of sample in the gap between the plate rim and the wall of the spheronization chamber. Further, the solubility of the drug had a major influence on pellet strength as reflected by their friability. For instance, as the level of the drug increased, the process became more difficult to carry out to completion. Thus, drug loads $\leq 50\%$ rendered pellets with good mechanical properties, but a drug load of 50% resulted in the most spherical, robust and reproducible pellets. On the contrary, a 75% drug load rendered more granular and dusty products and thus, they were not suitable for the

pelletization process (fig. 1). Since VH has a high water solubility it rendered pellets having lower friability values than those given by the CBZ pellets. Thus, it is expected a sufficient mechanical resistance for VH pellets to withstand handling and transportation. On the other hand, no significant changes were observed in pellet densification with increasing drug loads.

Further, all pellets showed a good uniformity of dosage indicating a homogeneous distribution of the drugs within the beads. The good drug homogeneity within the pellets is explained during the pelletization process when the powder was moistened drawing the primary particles of the drug: excipient mixtures together to form a ternary system (air-water-solid) having mobile liquid bridges. The effect of the initial particle size of the drug: excipient mixtures in the

pelletization process is considered negligible since it remained of $\sim 150 \mu\text{m}$. Further, the amount of water needed for the wet massing process only depended on the level of drug in the powder mixture allowing for the formation of large particles by random collisions. This mechanism required a constant moisture level on the surface of the particles.

Possibly, the addition of successive fragments produced by size reduction of powder mixtures onto the surface granules took place, allowing for a slow pellet consolidation rate. Further, a decrease in the number of collisions led to a reduction in the growth rate of the pellets and finally in the transfer rate of materials from bead to bead, especially in powder mixtures having high drug levels.

Table 1: Effect of drug loading on pellet properties

Load (%)	Wetting level (ml)	Ar* (mm)	Per* (mm)	FD*	Cir*	AR*	R*	CU (%)	Y (%)	Fr (%)	FR* (g/s)	BD* (g/cm ³)	TD* (g/cm ³)	MC (%)	Comp*
VH															
10	23	0.41±0.12	2.39±0.46	0.78±0.15	0.87±0.07	0.78±0.12	0.80±0.12	99.3	17.4	1.7	105.6±4.0	0.36±0.01	0.39±0.0	5.6	12.6±1.0
25	18	0.39±0.22	2.35±0.67	0.79±0.23	0.83±0.07	0.79±0.11	0.80±0.10	100.4	17.6	2.0	95.5±2.2	0.34±0.0	0.39±0.0	6.8	12.2±0
50	15	0.32±0.21	2.18±0.76	0.74±0.25	0.8±0.11	0.74±0.10	0.76±0.12	99.2	17.0	2.2	103.7±3.1	0.35±0.01	0.39±0.01	6.6	12.8±1
75	10	0.25±0.24	1.84±0.84	0.65±0.29	0.8±0.1	0.70±0.09	0.73±0.14	98.9	2.8	8.1	11.8±0.2	0.37±0.01	0.44±0.0	2.2	12.2±3
CBZ															
10	26	0.49±0.07	2.63±0.83	0.90±0.26	0.82±0.12	0.74±0.13	0.76±0.13	100.1	16.7	2.6	67.1±1.7	0.38±0.02	0.42±0.0	4.4	12.0±2.0
25	22	0.32±0.04	2.39±0.09	0.79±0.03	0.79±0.12	0.71±0.12	0.74±0.13	99.0	14.9	3.6	35.2±1.0	0.32±0.0	0.39±0.0	4.8	16.6±0.0
50	18	0.36±0.26	2.32±0.95	0.81±0.3	0.78±0.14	0.69±0.2	0.73±0.14	98.7	19.3	6.6	27±2.1	0.32±0.0	0.38±0.0	6.4	20.0±0.0
75	15	0.21±0.02	1.69±0.71	0.61±0.32	0.79±0.13	0.67±0.2	0.71±0.15	100.1	0.71	23.5	2.1±0.0	0.34±0.0	0.53±0.0	5.1	26.3±0.0

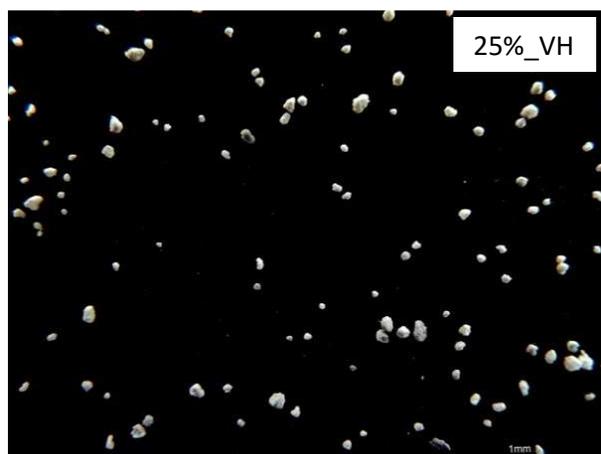
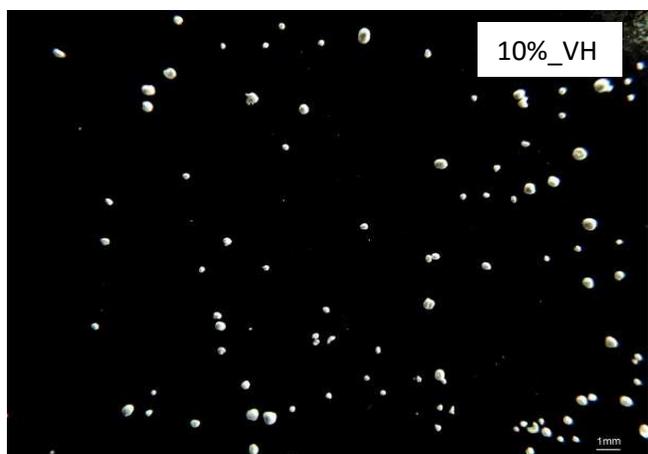
Error bars correspond to the standard deviation of 3 replicate. VH: verapamil. HCl, CBZ: Carbamazepine, Ar: Area, Per: perimeter, FD: Feret diameter, Cir: circularity, AR: aspect ratio, R: roundness, Sol: solidity, Y: yield, BD: bulk density, TD: tap density, M: mass, FR: flow rate, Fr: Friability, MC: moisture content, Comp: compressibility. Operational conditions of 6Hz, 480 s and 100% wetting level, *data given in mean±SD

Further, VH pellets presented a compressibility of $\sim 12\%$, which was associated to the high flowability values (95-106 g/s). This behaviour was due to the combined effect of their spherical shape, smoother surface and narrow particle size distribution. Conversely, CBZ pellets exhibited a low flowability (27-67 g/s), and a larger compressibility.

This outcome was attributed to the roughly surface and their highly irregular morphology as reflected by the shape descriptors such as aspect ratio, circularity and roundness. Further, size descriptors such as particle size, perimeter and the projected area of the pellets decreased as the drug load increased. This was

attributed to the lower amount of water needed to form a wet mass with sufficient plasticity to create pellets as explained previously.

Once this critical water mass was exceeded a non-processable sticky mass was formed. On the contrary, as the drug load decreased, a larger amount of water was required due to the major contribution of MCCII. For this reason, pellets having drug loads lower than 50% were highly spherical, less porous, larger in size, and had the best flowability and mechanical properties. In general, the 50:50 MCCII: drug ratio was selected as optimal since larger drug loads caused a major detriment on pellet properties.



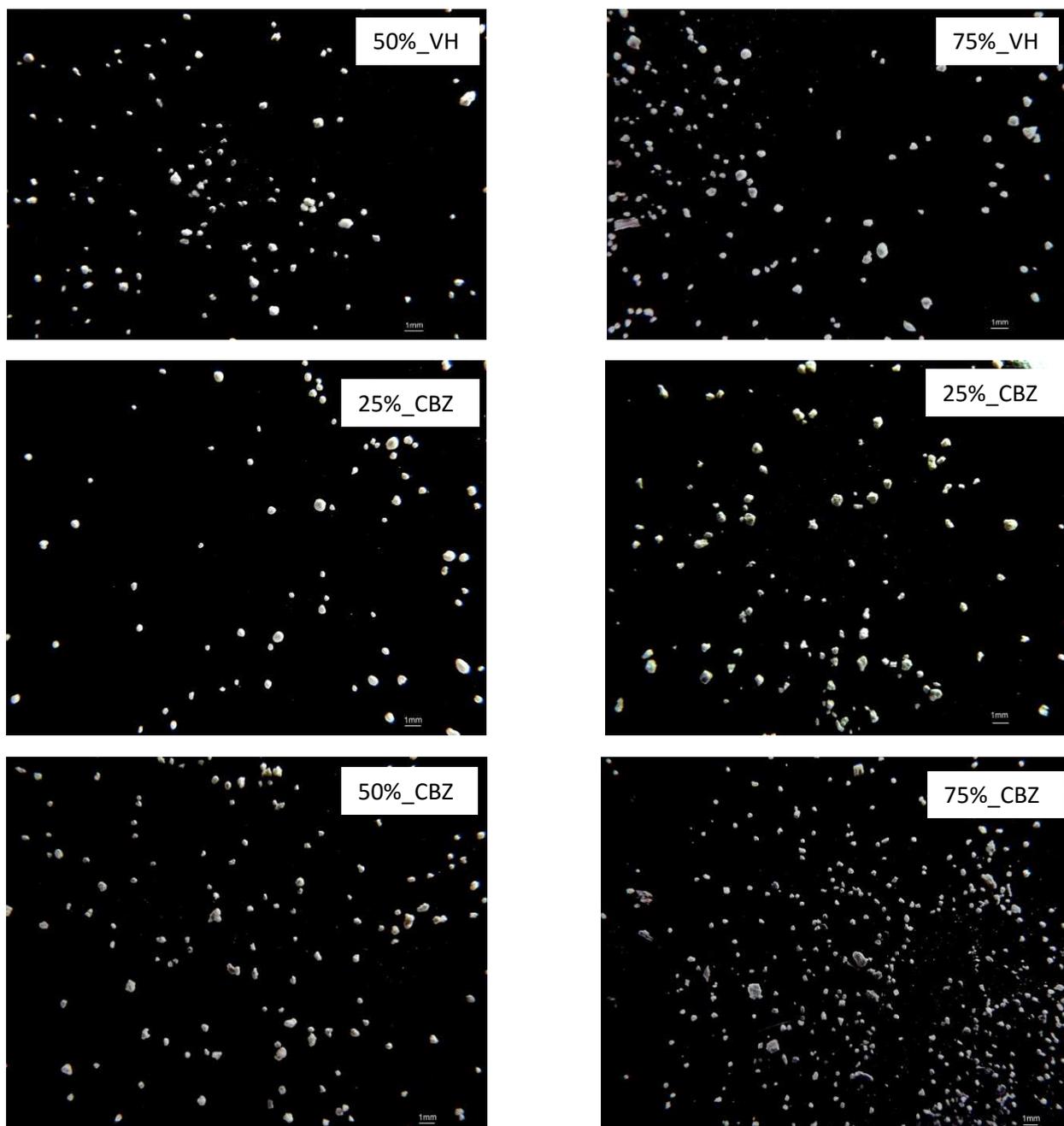
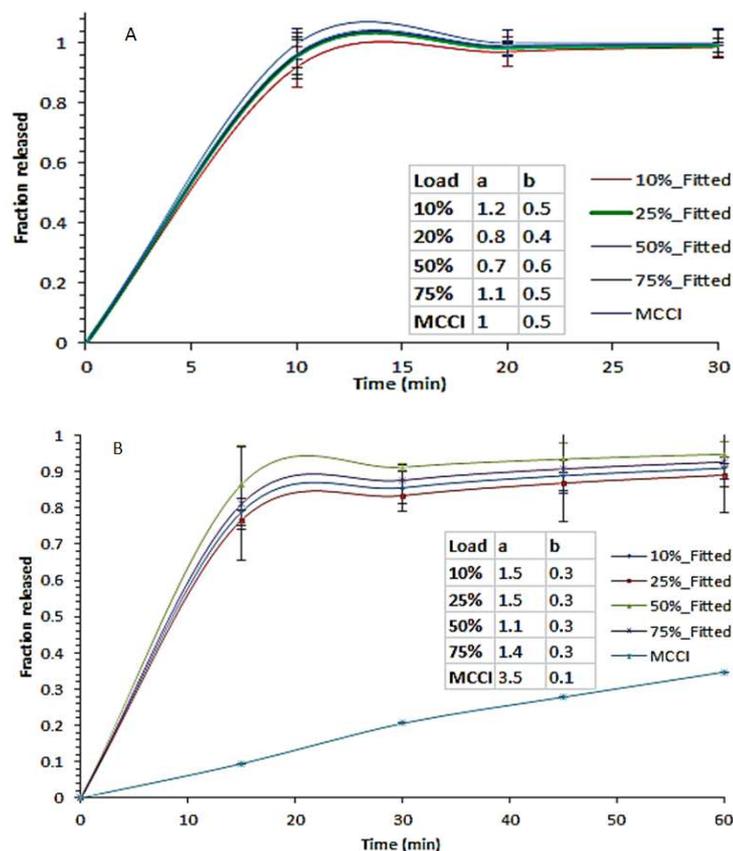


Fig. 1: Micropictures of beads produced under different drug loads. VH, verapamil HCl; CBZ, carbamazepine

Drug release properties

The drug release kinetics from the beads was determined by *in vitro* experimental studies. As clearly appreciable, the high aqueous solubility of VH (83 mg/ml) favored the rapid release behaviour from the pellets as compared to that from CBZ beads. For this reason, the initial segment of the VH curves is steeper. Further, VH samples were able to release at least 80% of the drug within 10 min regardless of the drug loading (fig. 2). Thus, VH exhibited a fast diffusion and release from the pellets. Moreover, MCCII pellets released at least 60% of CBZ within 15 min. Therefore, the drug release profiles were highly dependent on the solubility of the drugs and the high affinity of MCCII for water molecules. For instance, VH was washed out from the pellets leaving the pores in the matrix by diffusion; concomitantly MCCII pellets drew water molecules into the particles causing a burst by

capillary action. In this case, MCCII acted as an insoluble matrix in which the eluting aqueous media penetrated the matrix causing drug diffusion into the surrounding environment for ultimate absorption. Further, no significant differences were observed among the release profiles of VH from MCCI and MCCII. Conversely, the CBZ release rates from MCCI pellets markedly diverged from those of MCCII pellets. In fact, the "b" and "a" values of MCCI were the smallest and the highest, respectively indicating a very low release rate. This is explained by the lower capability of MCCI for water wicking, which caused a slowing pellet disintegration and hence, a sluggish drug dissolution. Further, the extent of release as reflected by the area under the curve of the release profiles revealed no significant differences among the VH (24-25 min) pellets, whereas for CBZ samples MCCII pellets showed higher values (42.4-47.3 min) as compared to the MCCI pellets (11.3 min).



A: Time scale dependence of the Weibull function, B: Indicates the shape of the profile, error bars indicate the standard deviation of three replicate

Fig. 2: Dissolution profiles of (a) Verapamil HCl and (b) Carbamazepine pellets, manufactured under different drug loads

CONCLUSION

MCCII had a high affinity for water molecules, and its wettability was slightly affected by the increasing levels of the drugs. Further, pellets having a high drug loading (>50g) caused an insufficient particle-particle or particle-plate interaction, which resulted in smaller and friable pellets having a poor flowability and irregular morphology. The 50:50 excipient: drug ratio rendered the highest drug loading having optimal mechanical and morphological characteristics. At these conditions, beads presented a spherical shape, a good flowability and plasticity. MCCII pellets also provided an immediate drug release profile for VH and CBZ mainly due to the high porosity and water affinity of MCCII as compared to MCCI.

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CONFLICT OF INTERESTS

Declared none

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