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Influence of Polymers on the Crystal Growth of Metformin Hydrochloride.

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Research Article

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ABSTRACT

Crystallization of metformin hydrochloride by solvent evaporation method was carried out in the presence of hydrophilic and hydrophobic polymers to investigate the influence of polymer in the agglomeration of the crystallites *in–vitro.* Transparent, prismatic shaped crystals (of size: 7 × 2 × 1.5 mm^3) were crystallized in hydrophilic polymer hydroxypropyl methylcellulose (HPMC) and long rod shaped crystal (of size: 20 × 2 × 1.5 mm^3) habits in hydrophobic polymer polyvinylpyrrolidone (PVP K30). The crystal structures were determined using single crystal X–ray diffraction method. Morphology studies revealed that the growth is prominent along *a*–axis and the prominent face is {001} for both the habits. Prismatic crystal habit is bounded by side faces {020} and corner faces {110}. FTIR spectral assignments were made and the fingerprint absorption band was identified. Thermal stability and thermal decomposition were analyzed using thermo calorimetry in the temperature range 30 -700°C.

INTRODUCTION

Crystallization from solution is the preliminary step in the production of pharmaceutical solids, which determine the physical properties of a material. Changes in the crystallization conditions can alter the crystal properties such as particle size, shape and purity, mechanical and thermodynamic properties. And these parameters will certainly contribute to the final tableting process. Thus crystallization is regarded as an eminent step to ensure the required characteristics and the desired pharmaceutical performance. Single crystals can be obtained by several methods such as: melt growth, solution growth, flux growth and hydrothermal synthesis. Amongst high temperature and low temperature solution growths, the latter is a simple and less expensive method for growing good quality single crystals. The growth of crystals from low temperature solution growth requires meticulous planning and patience and involves weeks or months' time. Obviously, the main advantages are lower growth temperature and better crystal quality with fewer defects compared to crystals grown directly from their melts [1]. Few drug crystals were grown by the authors recently [2,3,4].

Metformin hydrochloride ($C_4H_{11}N_5$.HCl) (1,1–Dimethylbiguanide hydrochloride), is an oral anti–hyperglycemic drug, belonging to the biguanide class. It has long been used in the management of non–insulin–dependent type 2 diabetes mellitus, particularly when the diet itself does not achieve weight and glycemia normalization [5]. Metformin hydrochloride (MH) is a hydrophilic drug and is commercially available under several trade names. They are metformin hydrochloride IR (immediate release) and metformin hydrochloride SR (sustained release) or metformin hydrochloride ER/XR–extended release) (MHSR). Direct compression method was widely used for the preparation of MHSR [6, 7]. Successful compaction depends on a combination of crystallinity-related properties and these should be better known by studying the physics of compaction of each drug [8]. Also, crystal habit and internal structure of a drug can disturb compressibility [9]. Formulation challenges were encountered in the tableting process of MHSR

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due to its compressibility, high dose and high water solubility [10]. Incorporation of drug in the matrix of hydrophilic and hydrophobic polymers has been successfully employed in the development of sustained release delivery systems to provide the desired release profile [11]. These polymers influence on the chemical stability, compactability and variability in physicochemical characteristics [12]. Several matrix formulations of MH have been experimented. However, the data related to crystallinity and compactability properties are not available in literature for MH [8]. Also the influence of polymers on the crystal habit and hence the dissolution character of the drug were not reported.

MH exists in two different polymorphs - the thermodynamically stable form (Form I) [13] and the metastable polymorph (Form II) [14] both having monoclinic structures. The main objective of the present study is to investigate role of HPMC and PVP on the crystalline form and characteristics of MH. Single crystal X–ray diffraction method was used to determine crystal structures. Morphology of the grown crystals was analyzed and its possible influence in tablet formulation is discussed. Fourier transform infrared (FTIR) spectroscopic analysis was made. Thermal stability and thermal decomposition were also analyzed under isothermal condition.

EXPERIMENTAL

Crystal growth

Metformin hydrochloride was purchased from USV Ltd, India. HPMC low viscosity grade (5 cps) and PVP K30 were purchased from S. D. fine chemicals Pvt. Ltd., Mumbai, India. Aqueous solutions of different concentration (0.1 - 1.0 M) of MH were prepared using the double distilled UV treated water and used as mother liquid. Crystal growth experiments were carried out as two sets. In case I, the hydrophilic polymer HPMC was dissolved in the mother liquid in a drug polymer ratio of 1:0.25 (w/w). This is for the study of crystal nature in MH plain formulation. In case II, hydrophilic polymer HPMC and hydrophobic polymer PVP K30 were dissolved in the mother liquid in a drug polymer ratio of 1:0.25:0.25 (w/w) to study the crystal nature in MHSR formulation. These liquids were transferred into the crystal growth vessels (petri dishes of 50 mm diameter) and maintained at an ambient temperature of ≈27°C in the modified crystal growth chamber for slow solvent evaporation.

X–ray diffraction analysis

Single crystal X–ray diffraction studies of the crystal habits were carried out using Enraf–Nonius CAD–4 Diffractometer, using MoKα (λ= 0.71073 Å). Cell parameters were obtained from least–squares refinement of the setting angles of 79 reflections.

Crystal morphology and packing

Crystal morphology was simulated using crystal structure data by the Bravais-Friedel-Donnay-Harker method (BFDH) [15] and the theoretical crystal morphology is compared with the as grown crystals. The faces of generated morph were indexed. Molecular packing was obtained by importing the CIF file of MH crystal into MERCURY 3.1 [16].

FTIR analysis

Pellets of MH crystals and potassium bromide (KBr) were prepared by applying a pressure of 15 tons in a hydraulic press. The pellets were scanned over a wavelength range of 400-4000 cm^{-1} using the SHIMADZU spectrometer FTIR-8400S at a resolution of 4 cm^{-1} and with a scanning speed of 2 mm/s. FTIR spectra was compared with the standard spectra of the functional groups [17].

Thermal analysis

Simultaneous thermogravimetric analysis (TGA) and differential thermal analysis (DTA) were carried out for the powdered sample of as grown MH crystals in the temperature range 25°C to 700°C with a constant heating rate of 10°C/min using Perkin Elmer, Diamond thermal analyzer. The crucible used was made of alumina which served as a reference for the sample.

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RESULTS AND DISCUSSION

Transparent, prismatic crystals of size: 7 × 2 × 1.5 mm^3 from aqueous solution of MH - hydrophilic polymer HPMC and transparent, long rods of size: 20 × 2 × 1.5 mm^3 from MH - hydrophilic polymer HPMC and hydrophobic polymer PVP K30 were crystallized within few days (Figure 1). For best crystal growth the concentration of MH was 0.75M. The prismatic habit [18] and rod habit [19] were reported in early literature. The lattice parameters are: a = 7.99(7) Å, b = 14.01(23) Å, c = 7.99(8) Å, β = 114.85(16)° and the space group is $P2_1/c$. These values agree well with the values reported in literature [13].

The faces of generated morph were indexed and the absence of {111} face contributed for the equivalence of theoretical crystal morphology with the as grown crystal of MH (Figure 2). Growth prominence along a–axis and {001} prominent face were the noted features of the grown crystals. Moreover the crystal was bounded by the side face {020} and corner face {110}.

The molecular packing diagram of MH is presented in Figure 3.The packing features were analyzed and correlated with crystal morphology. The title compound crystallized in centrosymmetric space group with each unit cell containing four molecules.

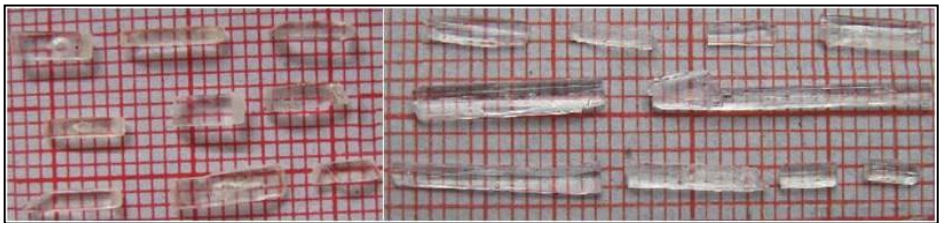

Figure 1: Prismatic and rod habits of metformin hydrochloride.

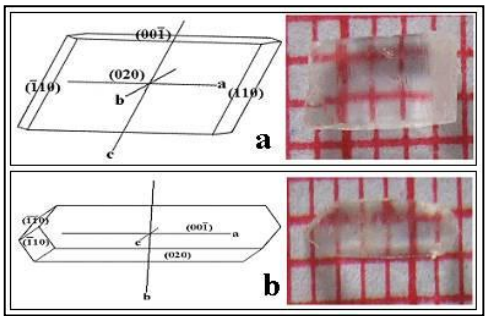

Figure 2: Crystal morphology and (a) viewed down b–axis (b) viewed down c–axis.

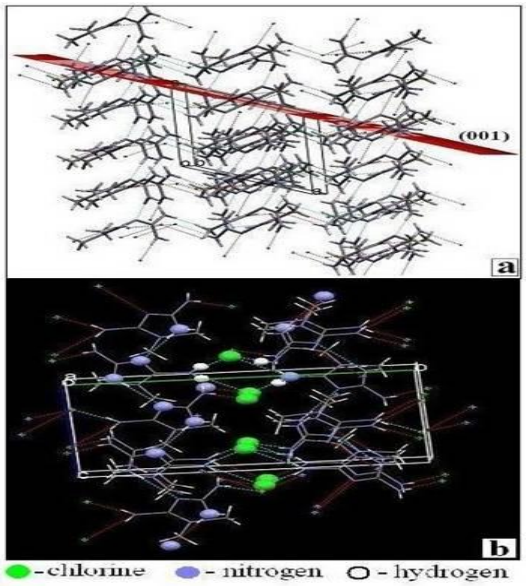

Figure 3: Packing diagram viewed down a) b–axis, b) a–axis.

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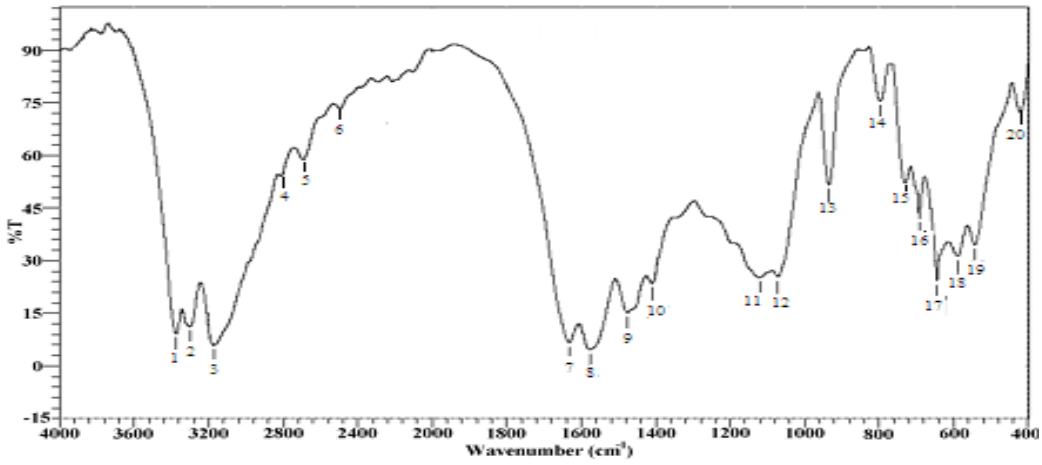

Figure 4: FTIR spectra of metformin hydrochloride.

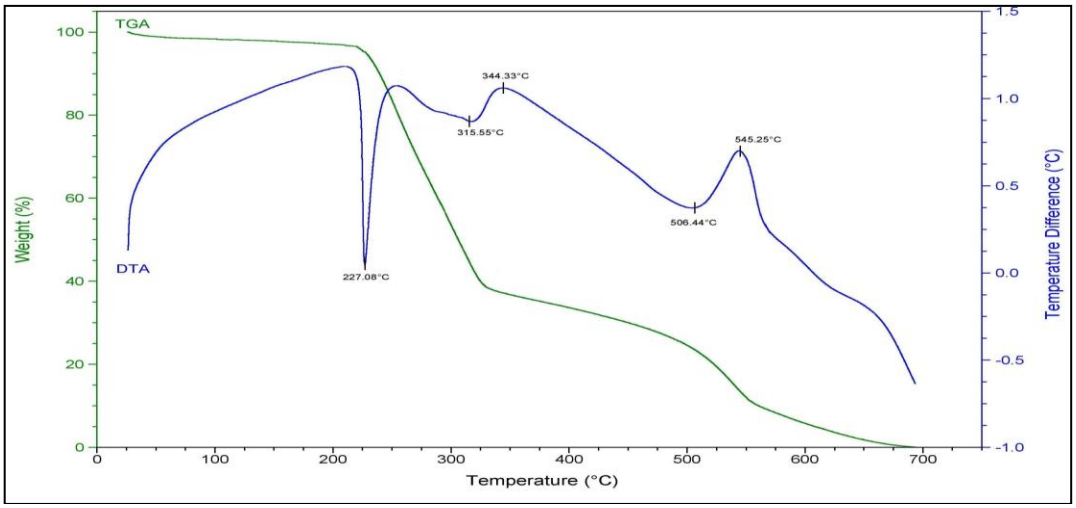

Figure 5: TGA/DTA of metformin hydrochloride.

Table 1: FTIR spectral data of metformin hydrochloride

Band	Wave number cm^{-1}	Tentative assignments
1	3375 s	ν_{as} (N-H)
2	3302 s	ν (N-H)
3	3173 vs	ν (N-H) + ν_{as}(C-H), γ (NH_2)
4	2826 w	ν_{as} (CH_3)
5	2702 w	ν (CH_3)
6	2488 w	H-Cl...N valence str.
7	1632 vs	C=N str + δ (NH_2)
8	1576 vs	C=N str
9	1477 s	CH_3 asym def
10	1410 s	CH_3 sym def
11	1121 s	ν (C-N)
12	1072 s	ρ (NH_2) + ρ (CH_3)
13	935 m	γ (C-H)
14	797 w	γ (C-H)
15	730 m	ω (NH_2)
16	692 m	ω (NH_2)
17	644 s	ω (NH_2)
18	590 s	β (C-N-C)
19	544 s	γ (C–N-C) + γ NH_2
20	431 w	γ (C-N-C)

ν_s – symmetric stretching; ν_{as} – asymmetric stretching; β– in plane bending,
δ_s – scissoring; ρ – rocking;γ – out of plane bending, τ– twisting; ω – wagging

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Table 2: Thermal decomposition of metformin hydrochloride

Stage	Temperature (°C)	Mass loss (%)	Equivalent molecule	Residue
I	30.0 – 239.9	10.28	NH_3	$C_2H_8N_4.HCl$
II	239.9 – 275.3	22.02	HCl	$C_2H_8N_4$
III	275.3 – 304.9	16.94	C_2H_4	$C_2H_4N_4$
IV	304.9 – 323.8	10.28	NH_3	C_2HN_3
V	323.8 – 585.4	33.23	HCN, N_2	C

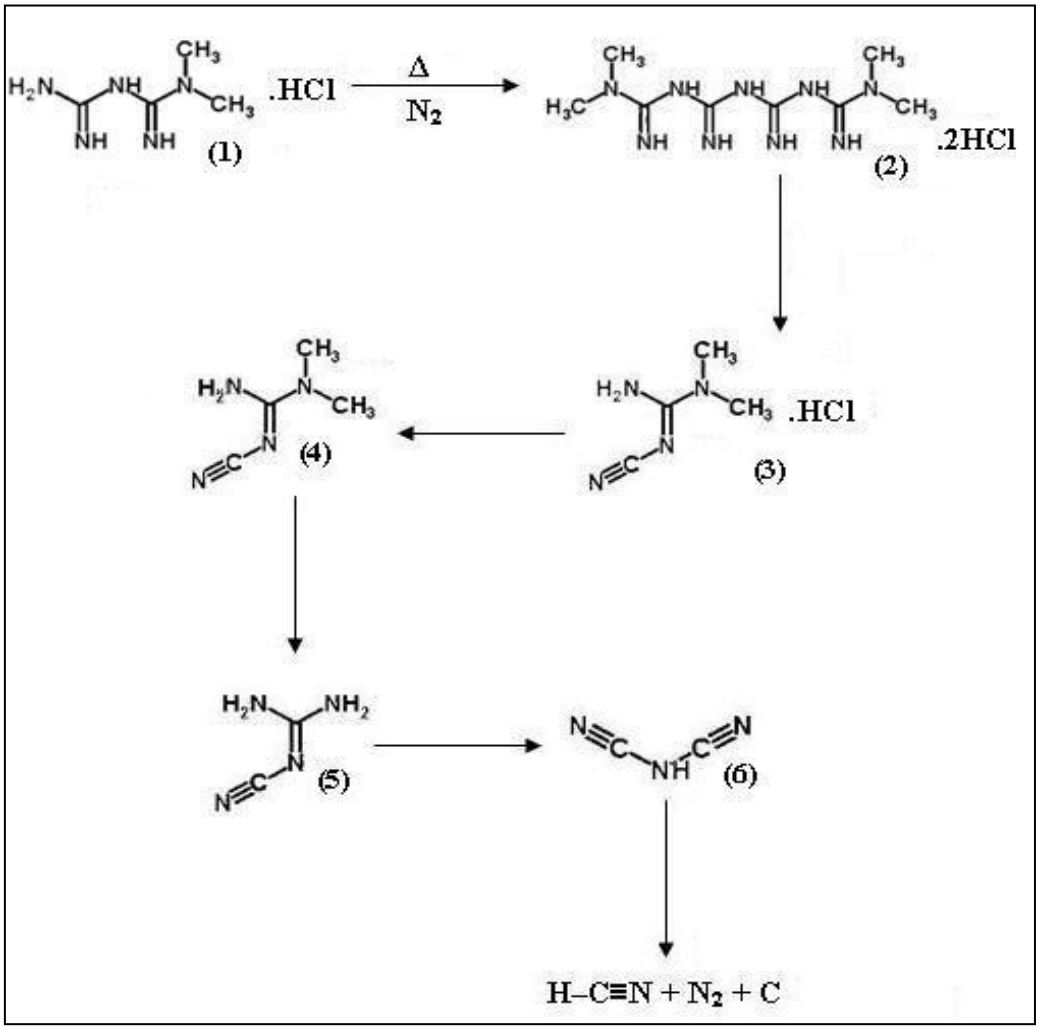

Figure 6: Decomposition scheme of metformin hydrochloride.

Crystal packing is due to four hydrogen bonds. Among these two N–H...Cl bonds and C–N...Cl bond are responsible for the agglomeration of the metformin molecules along the *a*- axis and so the growth prominence along this direction is observed in the crystal. The zigzag C–N...N bonds woven between neighboring molecules contributes for the formation of chain along *c*- axis. Hence sheets parallel to *c*- axis stacked along *a*–axis are formed resulting in the formation of the prominent face {001} in the crystal. This can be visualized in Figure 3a.

During crystallization process, fast growing faces normally grow out of existence; leaving the crystal bounded by the slowest growing faces. The growth rate of a face is directly proportional to its attachment energy [20]. Thus larger the attachment energy faster the growth rate and hence it has less importance with the morphology [21]. The attachment energies were calculated using the Miller indices and unit cell dimensions [22]. The calculated attachment energies of the faces {111}, {110}, {020} and {001} are 0.243, 0.155, 0.143 and 0.139 respectively. Hence the attachment energies of the faces are E_{111} >

$E_{110} > E_{020} > E_{001}$. Thus the prominent face is {020} for both the habits and the least prominent face {111} goes out of existence.

Crystals harvested from case I, had well defined prismatic structure and case II were long rods. The habitual modification of metformin hydrochloride may be attributed to the presence of the polymers. Generic MH drug consists of hydrophilic polymer (HPMC) only. The hydrophilic polymer attracts water molecules of the solvent and favours saturation, thus allow the crystal to grow up to critical size. MHSR drug consists of both hydrophilic (HPMC) and hydrophobic polymer (PVP). The hydrophobic polymer enhances crystallization by repelling water molecules making hydrophilic polymer to absorb more water. Hence the metformin crystals grow as long rods.

The prismatic well defined morphology will be more suitable than the long platy or rod types for tableting, to overcome manufacturing difficulties such as flowability, sticking to punches and compaction. Hence for tableting of MHSR by wet process the hydrophilic polymer may be mixed in the slurry to favour crystallization of prismatic MH crystals that suits for compaction. Hence hydrophobic polymer may be applied as outer coat by spray technique than impregnating into the tablet. This procedure may also be useful for all sustained release tablets.

The FTIR spectrum of MH crystal is presented in Figure 4. Absorption peaks of very strong intensity appeared in the region of 3173, 3302 and 3375 cm^{-1}, respectively because of N-H asymmetric and symmetric stretching vibrations. The peak at 3172 cm^{-1} is broad as it overlaps with that of C-H asymmetric vibrations. Intense absorption bands at 1632 cm^{-1} and 1576 cm^{-1} due to C=N stretching vibrations in biguanides are the fingerprints. Methyl stretching vibrations of aliphatic compounds were observed at 1477 cm^{-1} and 1410 cm^{-1}. C-N stretching of aliphatic diamines contributes absorption bands of weak intensity and occurs in the region of 1220-1020 cm^{-1}. These bands were noted at 1121 cm^{-1} and 1172 cm^{-1}. The absorption bands appearing in the lower wave number region (900-400 cm^{-1}) will be generally due to wagging, twisting, rocking, scissoring, bending or of stretching vibrations in inorganic molecules. C-H out of plane bending (935 cm^{-1}, 737 cm^{-1}) and NH_2 wagging (730 cm^{-1}, 692 cm^{-1} and 644 cm^{-1}) vibrations belong to this category. C-N-C ligand gives out absorption bands in the region 600-400 cm^{-1}. The bands due to out of plane bending mode were observed at 544 cm^{-1} and 431 cm^{-1}. The high intensity of the former band is attributed to the overlap of bands with that of NH_2 molecule. All the tentative assignments are listed in Table 1.

The DTA profile of MH (Figure 5) shows three endothermic peaks (227.08°C, 315.55°C and 506.44°C) and two exothermic peaks (344.3°C and 545.25°C). The first endothermic peak at 227.08°C indicates the melting point of metformin hydrochloride as noted in the literature [23].

The TGA quantifies that the mass loss happened in five stages. The first mass loss (Δm = 10.28%) at 239.9°C is attributed to the release of NH_3 molecule from the title compound 1,1-Dimethylbiguanide hydrochloride (1) and an exothermic trend affirms this dissociation. An unstable intermediate compound N-[N-(N, N-dimethylcarbamimidoyl)carbamimidoyl]- N,N-dimethylimidodicarbonimidic diamide dihydrochloride (2) and an end product 1,1-dimethyl-2-cyanoguanidine hydrochloride (3) may result in this process. The formation of compound (2) may be justified by the mass loss 5.1% equivalent to half molecule of NH_3 evolved due to dimerization of compound (1). Further heating results in a loss of 22.02% with the elimination of HCl molecule at 275.3 °C from the compound (3). The liberation of C_2H_4 molecule contributes a mass loss of 16.94% at 304.9°C and the compound (5) cyanoguanidine ($C_2H_4N_4$) may be formed. This compound decompose to become dicyanamide (C_2HN_3) (6) and NH_3 resulting with a mass loss of 10.28% at 323.8°C. Further heating results in a mass loss 16.32% (HCN) and 16.91% (N_2) at 585.4°C and leaves carbon as residue. The estimated mass loss is presented in Table 2 and the decomposition scheme is depicted in Figure 6.

CONCLUSIONS

Transparent, prismatic crystals and transparent, long rods were crystallized in the presence of hydrophilic polymer HPMC and hydrophobic polymer PVP respectively from aqueous solution of MH by natural evaporation method. Monoclinic forms of the crystals were confirmed using single crystal X–ray diffraction method. Morphology study showed that {001} is the prominent face and the growth is prominent along *a*–axis. Functional groups and modes of vibrations, the fingerprint absorption bands of metformin hydrochloride were identified using FTIR spectroscopy. The thermographic profile of metformin hydrochloride revealed that the biguanide structure is maintained up to 240°C and hence the drug is thermally stable.

Another useful result is the hydrophobic polymer in MHSR may favour the crystal growth of long rods in wet process. Since the prismatic well defined morphology will be more suitable than the long platy or rod types for tableting, hydrophilic polymer may be mixed in the slurry and hydrophobic polymer be applied as outer coat than impregnating into the tablet.

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