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7        Drug – smectite clay amorphous solid  
8        dispersions processed by Hot Melt Extrusion  
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24 ***Abstract***

25 The aim of this study was to investigate suitability of natural and synthetic smectite clay  
26 matrices as a drug delivery carrier for the development of amorphous solid dispersions (ASD).  
27 Indomethacin (IND) was processed with two different smectite clays, natural-magnesium  
28 aluminium and synthetic-lithium magnesium sodium silicates, using Hot Melt Extrusion  
29 (HME) to prepare solid dispersions. Scanning electron microscopy (SEM), Powdered X-ray  
30 diffraction (PXRD), Differential scanning calorimetry (DSC) were used to examine the  
31 physical form of the drug. Energy dispersive X-ray spectroscopy (EDX) was used to investigate  
32 the drug distribution and Attenuated Total Reflectance-Fourier transform infrared (ATR-  
33 FTIR) spectroscopic analysis was done to detect any chemical interaction between these two  
34 kinds. Both, PXRD and DSC analysis showed that drug-clay solid dispersion contained IND  
35 in amorphous form. Energy dispersive X-ray (EDX) analysis showed a uniform IND dispersion  
36 in the extruded powders. ATR-FTIR data presented possible drug and clay interactions *via*  
37 hydrogen bonding. *In-vitro* drug dissolution studies revealed a lag time of about two hours in  
38 the acidic media and a rapid release of IND at pH 7.4. The work demonstrated that preparation  
39 of amorphous solid dispersion using inorganic smectite clay particles can effectively increase  
40 the dissolution rate of IND.

41 **KEYWORD:** Indomethacin, clay, hot-melt extrusion, dissolution, solid dispersion.

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## 50 INTRODUCTION

51 To date, numerous drug molecules have been discovered with higher molecular weight, greater  
52 lipophilicity, and minimal water solubility which often cause difficulties during their  
53 pharmaceutical manufacturing process (1,2). Primarily, these factors are liable for an  
54 inadequate drug dissolution and their limited bioavailability. At the same time, this rise of  
55 poorly water soluble drugs also pushed for innovative strategies to overcome solubility related  
56 issues *i.e.* salt formation (3), co-crystals (4), pro-drugs formation (5), solid lipid nanoparticle  
57 (6), amorphous solid dispersion (7) *etc.* Among these, amorphous solid dispersion- invented  
58 by Sekiguchi and Obi in 1961, has shown promising results for improving dissolution rates of  
59 poorly water soluble compounds (8). This technique allows to disperse an insoluble drug in a  
60 water soluble carrier at molecular level, enabling it to greatly enhance the total specific surface  
61 area which ultimately increases the dissolution rate and bioavailability.

62 Clays are water soluble silicate compounds, generally used as an excipient in pharmaceutical  
63 formulations *i.e.* lubricant, desiccant, disintegrant, diluent, binder, opacifier, as well as  
64 emulsifying, thickening, isotonic agent, anticaking agent, flavour corrector and carrier of active  
65 ingredients *etc.* (9–11). Among many varieties, smectite clays are particularly well known for  
66 their water solubility, dispersivity, swelling capacity and relatively high specific surface area  
67 (12). Takahashi and Yamaguchi believed that swelling ability of clay silicates and their  
68 complex formation ability is beneficial to act as a drug carrier and solubilise poorly water-  
69 soluble drugs (13). Authors prepared griseofluvin-clay hybrids with less than 5% clay complex  
70 which demonstrated higher solubility compare to the pure drug. Goncalbes *et al.* also explored  
71 the use of phyllosilicate clay mineral to increase the solubility of olanzapine (14). Prepared  
72 phyllosilicate and olanzapine complex showed around 50% increase of dissolution rate within  
73 first 60 minutes (min) of the study.

74 Smectite clays such as natural-Veegum (VF) and synthetic-laponite (LP) are also widely used  
75 in the pharmaceuticals as stabilising and suspending agent, rheology modifier as well as texture  
76 enhancer (15,16). Primarily, these high swelling clays contain Na<sup>+</sup> ions in between their  
77 interlayer spacing, enabling them to adsorb up to 32 layers of water molecules (17). Adebisi *et*  
78 *al.* found that VF increases the dissolution rate of theophylline from the tablet matrices (15).  
79 LP nanoparticles were used to enhance the solubility of itraconazole upto 75%, reported by  
80 Jung *et al.* (18). Such investigations of clay mineral clearly indicating possibilities to improve  
81 the dissolution rate of indomethacin (IND). The rationale for using clay silicates as a  
82 dissolution rate enhancing component was the hydrophilic nature of silica particles. Silica  
83 particles contain abundant hydroxyl groups and exceptionally high specific surface area that  
84 enables drug particles to interact instantaneously with the water molecules through hydrogen  
85 bonding. Bahl D. *et al.* co-grinded also IND with pharmaceutical silicates to enhance the  
86 dissolution rate of the drug (19).

87 IND is a non-steroidal, anti-inflammatory drug belongs to BCS class II category with a  
88 solubility of only 0.937 mg/L in water (20). Such a water insoluble drug often shows low  
89 absorption and poor bioavailability. Also limited solubility of this drug may also increase the  
90 residence time in the gastro-intestinal tract which may irritate the gastric mucosal layer (21).  
91 Hence, IND formulation preparation with an improved dissolution rate is at utmost importance  
92 to the pharmaceutical manufacturing industry.

93 The use of hot melt extrusion as a processing technology for the development of amorphous  
94 solid dispersions is well – known in pharmaceutical industry. HME possesses many advantages  
95 such as cost effective, high throughput, minimal waste loss and solvent free processing  
96 technology. There are numerous studies where HME has been employed for preparing  
97 amorphous solid dispersion with improved dissolution rates of poorly water soluble  
98 compounds. Although polymeric solid dispersions of IND have been reported previously (22),

99 the efficacy of clay minerals as an inorganic carrier is yet to be explored. Hence, the current  
100 study investigates the feasibility of natural and synthetic smectite clay silica particles for solid  
101 dispersion of IND to improve the dissolution rates using TSE.

## 102 **MATERIALS AND METHODS**

### 103 **Materials**

104 Veegum F<sup>®</sup> (Magnesium aluminium metasilicate) and Laponite RDS<sup>®</sup> (Lithium magnesium  
105 sodium silicate) clay minerals were kindly donated by Vanderbilt minerals llc. (USA) and BYK  
106 additives ltd. (Germany) respectively. Indomethacin was purchased from Tokyo chemical  
107 industries (Japan), with a purity of >98.0% and all the reagents were used as received. Other  
108 chemical reagents such as hydrochloric acid, di-Potassium hydrogen orthophosphate,  
109 Potassium di-hydrogen phosphate, acetonitrile (HPLC grade), Ortho-phosphoric acid were  
110 purchased from Fisher scientific UK and used as received.

### 111 **Continuous processing of ASD using HME**

112 IND formulations shown in Table I. were blended using a Turbula TF2 Mixer (Switzerland)  
113 for 10 min. Then solid dispersions of IND were prepared using a 10 mm Rondol Microlab twin  
114 screw extruder (France) with a 25:1 L/D ratio. Standard screw configuration with two kneading  
115 zones and three conveying zone was used to disperse solid drug materials in the clay matrices  
116 (shown in Fig. 1). The extruder barrel has five different heating zones where 80- 140- 170-  
117 170- 30 °C (from feed to die) temperature were used to established ASD. Extrusions were  
118 processed using 25% or 0.1 kg/hr feed rate with a screw speed of 50 rpm.

119 **Table I.** Formulations used for continuous solid dispersion using HME

<b>Formulation</b>	<b>IND (%)</b>	<b>VF (%)</b>	<b>LP (%)</b>
VIN-20	20.0	80.0	-

VIN-40	40.0	60.0	-
LIN-20	20.0	-	80.0
LIN-40	40.0	-	60.0

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\*V- Veegum F, L- Laponite RDS, IN- Indomethacin



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122

**Fig. 1.** Photograph of screw configuration.

123 **Morphology analysis of extrudates**

124 SEM was used to study the surface morphology of the prepared extrudates. All the samples  
 125 were mounted on an aluminium stub using adhesive carbon tape and placed in a low humidity  
 126 chamber prior to analysis. Samples were then examined using a Cambridge Instruments (S630,  
 127 UK), SEM operating at an accelerating voltage of 1.0 kV. Particle size distributions of the  
 128 extruded powders were determined using a Mastersizer 2000 laser diffraction instrument  
 129 (Malvern Instruments, UK) with a dry powder sample dispersion accessory (Scirocco 2000)  
 130 and pressure at 2 bar and a vibration feed rate of 50%. Samples were examined in triplicate and  
 131 Mastersizer 2000 software was used for data evaluation.

132 **PXRD analysis**

133 Crystalline structure of the pure and extruded materials were investigated using a Bruker D8  
 134 Advance (Germany) X-ray powder diffractometer in 2-theta mode. The instrument was  
 135 equipped with a copper anode at 40 KV, parallel beam Goebel mirror, 0.2 mm exit slit and a  
 136 LynxEye position sensitive detector with 3° opening (Lynxiris at 6.5 mm). Each sample was

137 prepared using a PMMA (Poly-methyl-methacrylate) sample holder which was scanned from  
138 2 to 56 °2θ with a step size 0.02 °2θ, counting time 0.1 s per step and a rotation of 15 rpm.

#### 139 **DSC analysis**

140 Thermal analysis were done using a Mettler-Toledo 823e (Switzerland) differential scanning  
141 calorimeter on the drug and extruded samples. About 4 mg of samples were placed in a sealed  
142 aluminium pan with pierced lids. Prepared samples were heated from 30 to 230 °C at a heating  
143 rate of 10 °C/min under dry nitrogen atmosphere.

#### 144 **ATR-FTIR analysis**

145 Pure drug, clays and extruded formulations were also separately compressed into a thin disk  
146 using a SPECAC hydraulic press and investigated using a Perkin Elmer Spectrum Two ATR-  
147 FTIR spectrometer (USA) between 450 and 4000 cm<sup>-1</sup> wavenumbers, with 10 scans at a  
148 resolution of 8 cm<sup>-1</sup>. Samples were then fixed onto an aluminium stub using double sided  
149 carbon adhesive tape for elemental analysis using Energy dispersive X-ray (EDX)  
150 spectroscopy.

#### 151 **EDX analysis**

152 EDX spectroscopy was obtained using a JEOL JSM- 5310LV (JAPAN) instrument.  
153 Micrographs were collected at 20 kV accelerating voltage, 20 mm working distance, 15 spot  
154 size and using a backscattered electron detector. Elemental mapping was also studied using an  
155 Aztec X-ray microanalysis system with X-Max<sup>N</sup> detector from Oxford instrument (UK).

#### 156 ***In-vitro* dissolution study**

157 Release of IND from the clay matrices were also examined using a Varian 705 DS (USA)  
158 paddle apparatus at 100 rpm and 37 °C. At first, 750 mL 0.1 N HCl solution of pH 1.2 were  
159 used to study the drug release for 2 hr. After that 150 mL of phosphate buffer was added and



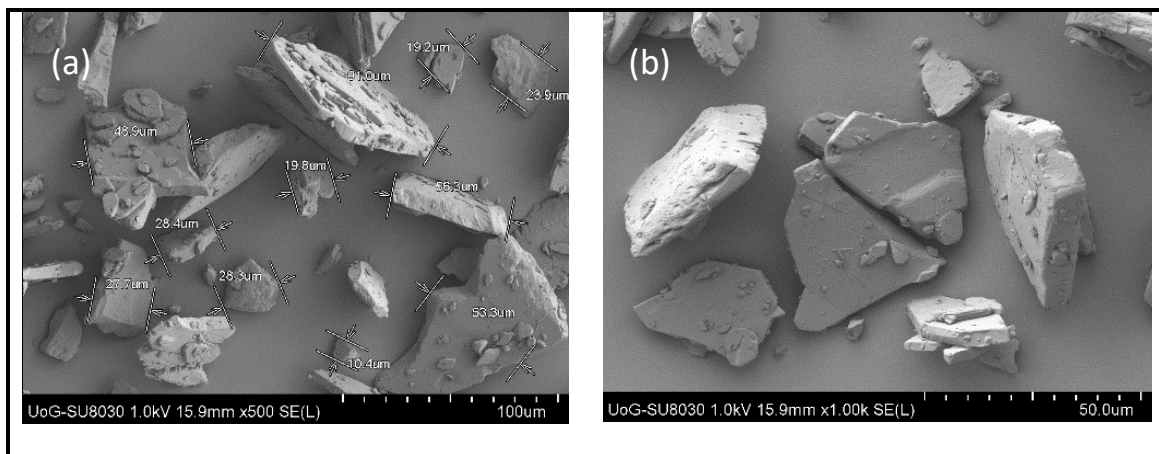
160 pH was adjusted to 7.4 using NaOH solution. Samples were collected at 15, 30, 60, 90, 120  
161 min time interval from both pH and dissolution studies were also performed in triplicate.  
162 Samples were then analysed using a high performance liquid chromatographic system provided  
163 by Agilent Technologies, 1200 series (USA). IND was analysed using a HYCHROME  
164 S50DS2-4889 (5×150×4 mm) column and an UV detector at a wavelength of 214 nm. The  
165 mobile phase were prepared using acetonitrile: water: Ortho-phosphoric acid (49.5: 49.3: 0.2  
166 v/v) and pumped at a flow rate of 1.5 mL/min. Abovementioned specification showed a 112 to  
167 114 bar of column back pressure with a retention time of  $3.00 \pm 0.1$  min. Calibration curve was  
168 also prepared using 20, 40, 60, 80 and 100 µg/mL concentrated ethanolic solution of IND.

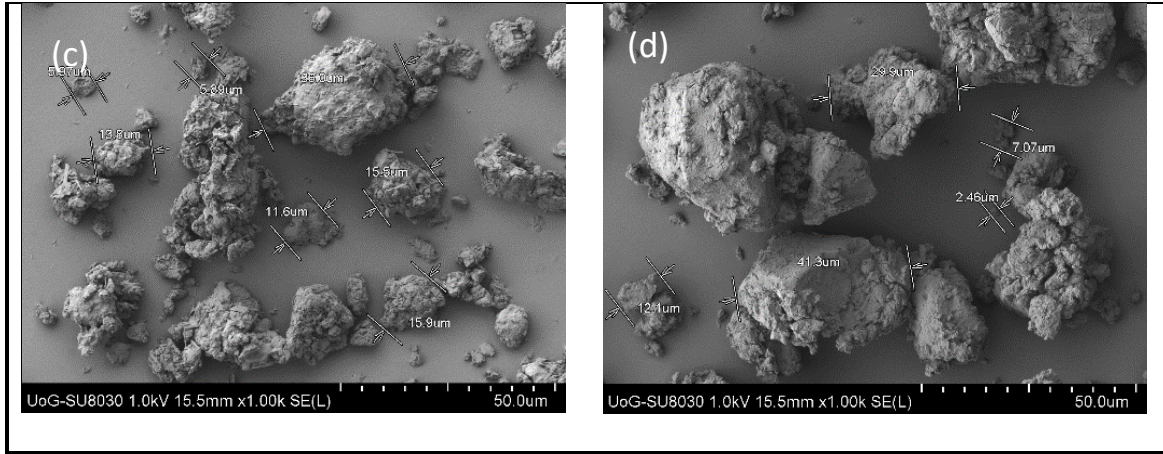
## 169 **RESULTS AND DISCUSSIONS**

170 In the current study, solid dispersions of IND in inorganic clay silicates were prepared by HME  
171 and the suitability of clay silicates were also investigated as a carrier for poorly water-soluble  
172 pharmaceutical actives. To optimise the processing conditions, various parameters such as  
173 temperature, screw speed, feed rate were taken into careful considerations. Extrusion  
174 temperature profile optimisation played a key role in the development of ASDs. Formulations  
175 were also designed carefully to investigate the efficiency of HME processing on layered clay  
176 silicates and drug molecules. Literature suggests, ASD prepared with HME technology  
177 contains amorphous form of drug particles with a higher Gibbs free energy (23,24). In this  
178 study, both natural and synthetic grades of hydrophilic smectite clays were used to increase the  
179 wettability of IND leading to an improved drug dissolution rate. The drug and clay ratio was  
180 further investigated to evaluate the effect on the dissolution rate improvement. The absence of  
181 the die during extrusion led to the formation of free-flowing extruded powders in the form of  
182 micro-particles which in turn reduced downstream processing. The powders were collected for  
183 further physicochemical characterisation with no need for milling.

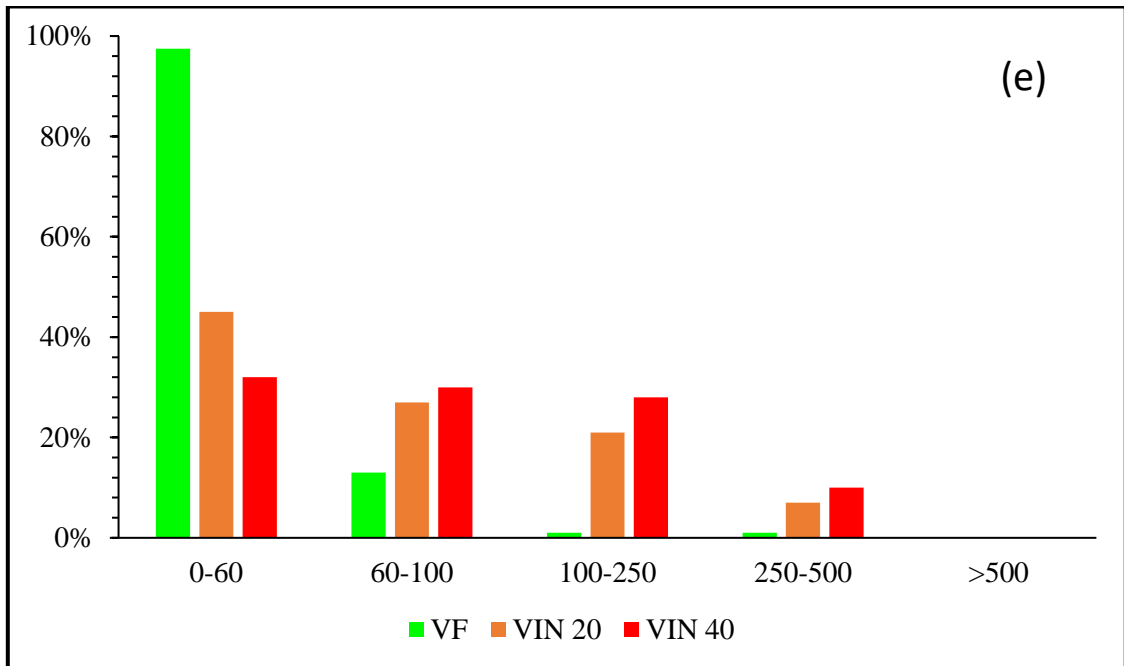
184 **Morphology analysis of extrudates**

185 The morphology of bulk drug and extruded formulations were analysed using SEM. Fig. 2. (a,  
186 b) shows bulk IND particles which present plate-shape morphology. On the other hand, in Fig.  
187 2. (c, d) the obtained solid dispersions showed the absence of crystalline IND as a result of the  
188 extrusion process optimisation. This suggests the adsorption of melted drug molecules in the  
189 silica porous network which not only facilitates the transformation of drug into amorphous  
190 state but also result in improved powder flowability for the development of the finished dosage  
191 form *i.e.* tablet preparation using direct compression method or capsules preparation (25). In  
192 addition, the extruded dispersions appear as granular micro-agglomerates due to the absence  
193 of the extrusion die. Extruded powders were then analysed using particle size analyser and  
194 results has been presented in Fig. 2. (e, f). As it can be seen a large percentage of fine particles  
195 was observed in the bulk clays prior to extrusion processing. In the drug loaded clays, a  
196 significant reduction of the fines was detected, and the formation of larger agglomerates took  
197 place in agreement with SEM analysis. In Fig. 2. e, can also be seen that higher drug loadings  
198 (40%) facilitated the formation of larger granules with sizes varying from 100 – 500  $\mu\text{m}$ .

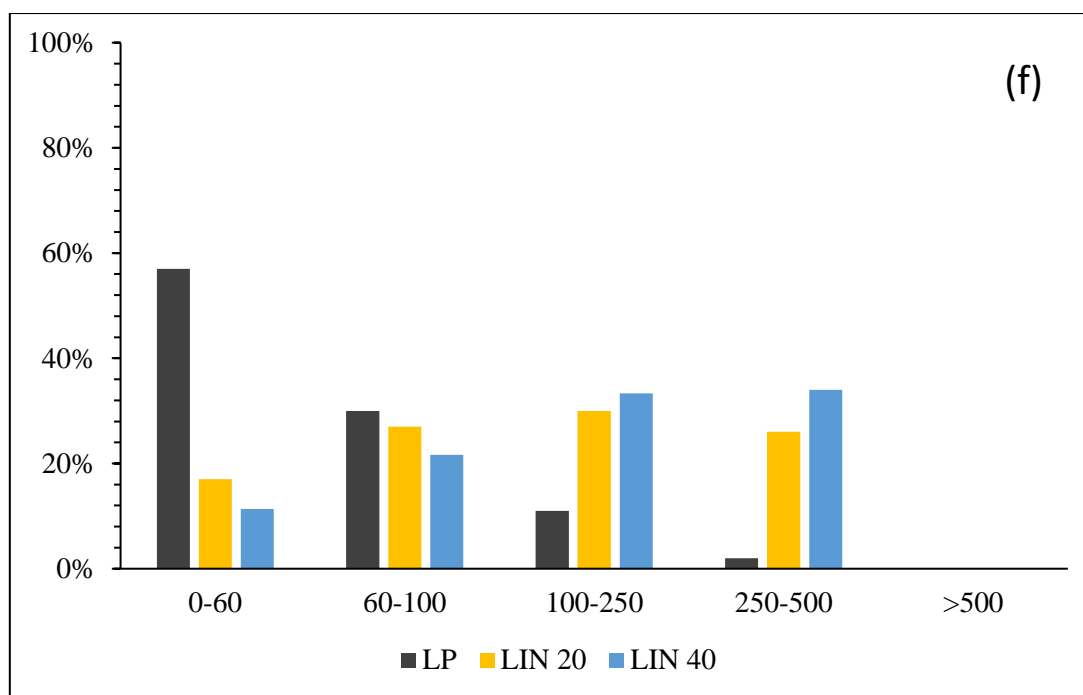




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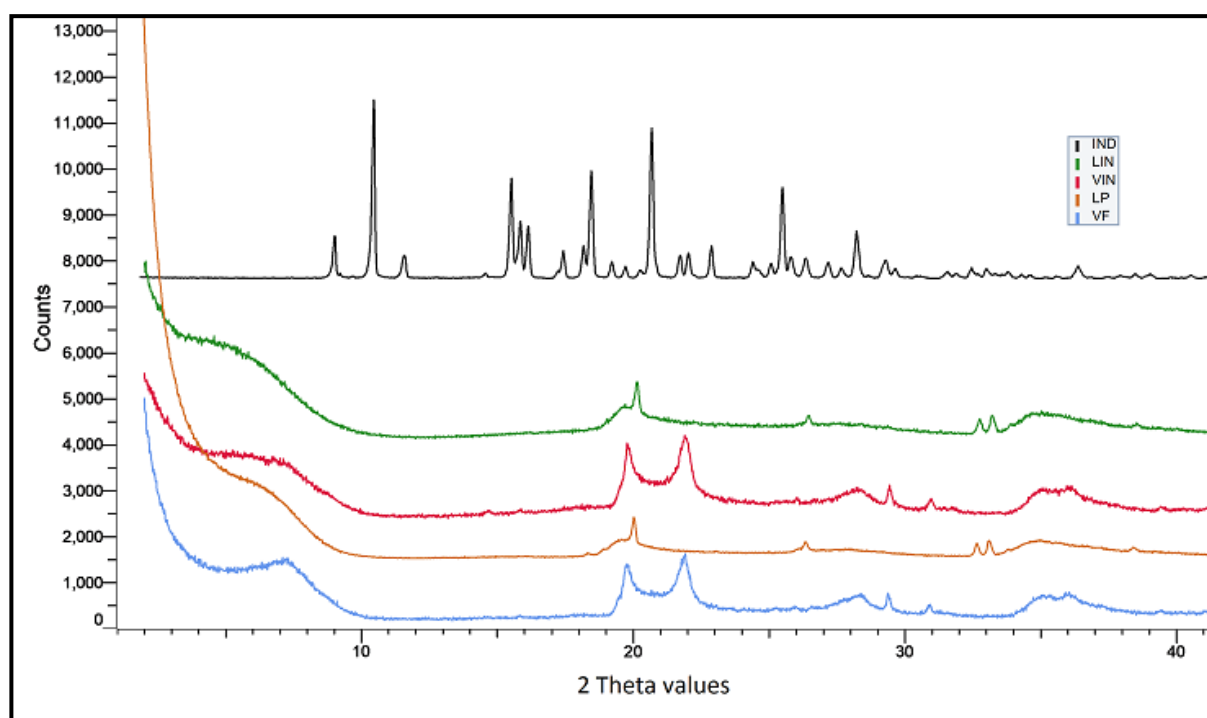
203 **Fig. 2.** (Top) SEM micrographs of (a-b) pure IND, c- VIN and d- LIN extruded formulations.

204 (Bottom) Particle size distribution of VIN, LIN extruded formulations against pure clay.

## 205 **PXRD analysis**

206 The physical state of the crystalline drug, clay and their extruded formulations were examined  
 207 using PXRD analytical technique and shown in Fig. 3. Diffractogram of crystalline IND  
 208 showed peaks with sharp intensity at 9.1, 10.6, 11.7, 15.8, 18.6, 20.8, 25.6 and 28.3 °2θ. Pure  
 209 clays, VF and LP also showed their primary peaks at 7.4, 19.9, 21.9 °2θ and 6.5, 20.1, 33.3 °2θ  
 210 respectively. Interlayer spacing for pure VF at 7.4 °2θ= 11.9 Å and LP at 6.5 °2θ= 13.6 Å was  
 211 found using Bragg's law ( $n\lambda=2d\sin\theta$ ). Although the interlayer spacing of anhydrous smectite  
 212 clay should be ~ 10 Å, presence of homogeneous water molecules increases the interlayer  
 213 spacing between two aluminosilicate sheets (26). The broad interlayer spacing also indicates  
 214 the poor organisation of silicate layers in the structure. PXRD pattern of VIN and LIN  
 215 formulations showed higher basal spacing compare to the pure clays. In particular, the basal  
 216 spacing of VIN was indistinguishable in obtained the diffractogram. The IND – VIN and IND  
 217 – LIN extruded formulation did not present any intensity peaks related to bulk IND. These

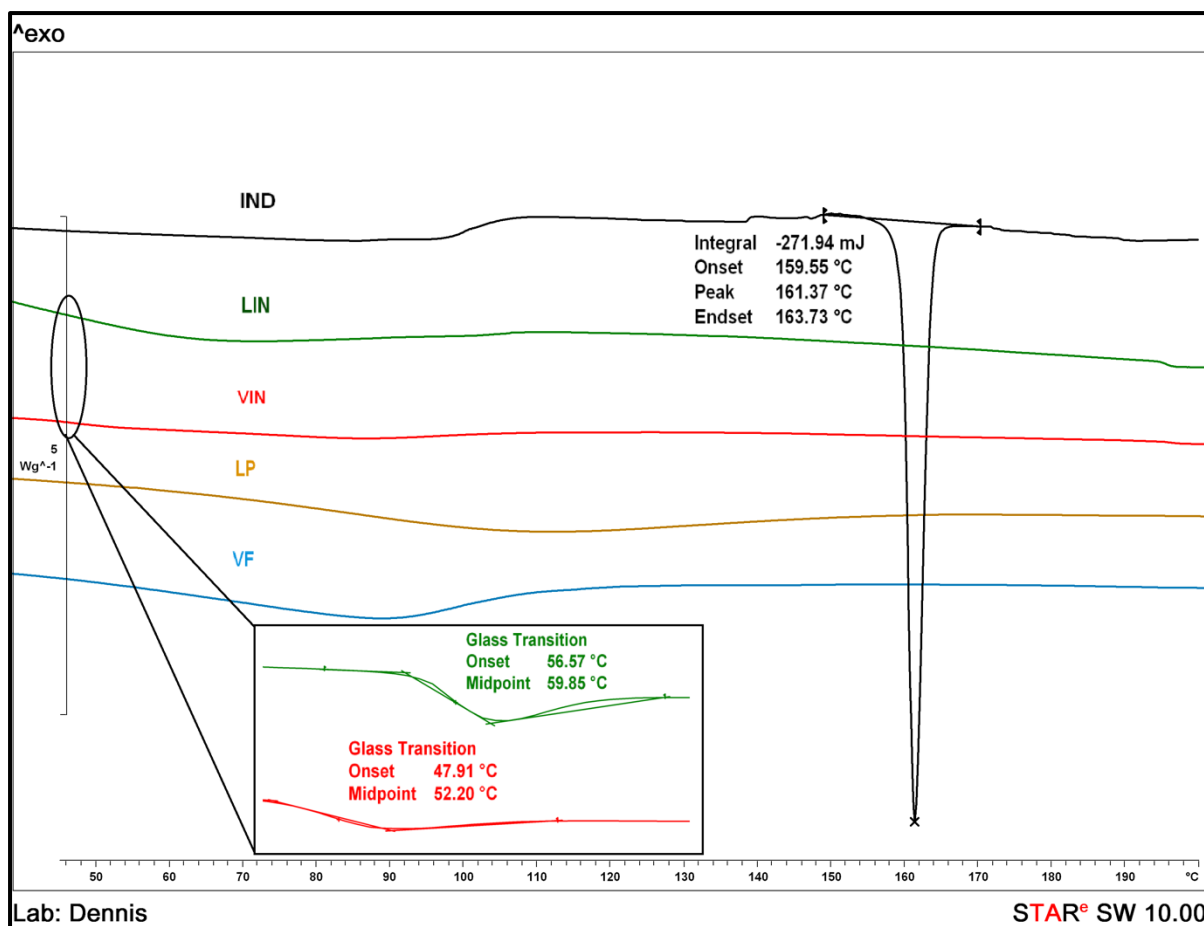
218 results suggest the formation of amorphous solid dispersions probably due to stronger  
219 interactions between the drug and the clay at molecular level. Interestingly, the extruded  
220 formulations appeared partially amorphous when extrusion temperatures were set below 160  
221 °C. Stability studies were also performed at 25 °C/ 60% RH for 12 months and showed that  
222 extruded IND-silicate dispersions were relatively stable with no more than 10±2% increase in  
223 their crystallinity compared to fresh extruded batches.



224  
225 **Fig. 3.** PXRD diffractograms of bulk IND, smectite clays and extruded formulations.

### 226 DSC analysis

227 Thermal transitions of bulk drug, clay and extruded formulations were studied using DSC  
228 analysis shown in Fig. 4. The IND thermogram showed a sharp endothermic peak at 162 °C  
229 representing the melting point of the pure crystalline IND (21,27). In contrast, both of the clays  
230 did not present any melting endotherms within the investigated temperature range. However,  
231 both VF and LP showed endothermic events at 35-125 °C and 35-165 °C respectively which  
232 corresponds to the removal of the surface bound water molecules from the clay (28).



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234

**Fig. 4.** Thermal transitions of pure IND, VF, LP, VIN and LIN extruded formulations.

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Similarly, thermograms of VIN and LIN extruded formulations presented water loss at 30-110

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°C with lower enthalpy values due to the HME processing at 170 °C. Fig. 4 also shows that the

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absence of IND melting endothermic peak in VIN and LIN formulations (22,27). Most

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importantly, the VIN and LIN thermograms presented endothermic events at 47.91 and 56.57

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°C respectively which might correspond to the drug's  $T_g$  where for the amorphous IND is

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around at 46 °C. However, the observed endothermic events showed a shift of  $T_g$  to higher

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temperatures which is not unusual and it has been reported that clays can shift glass transitions

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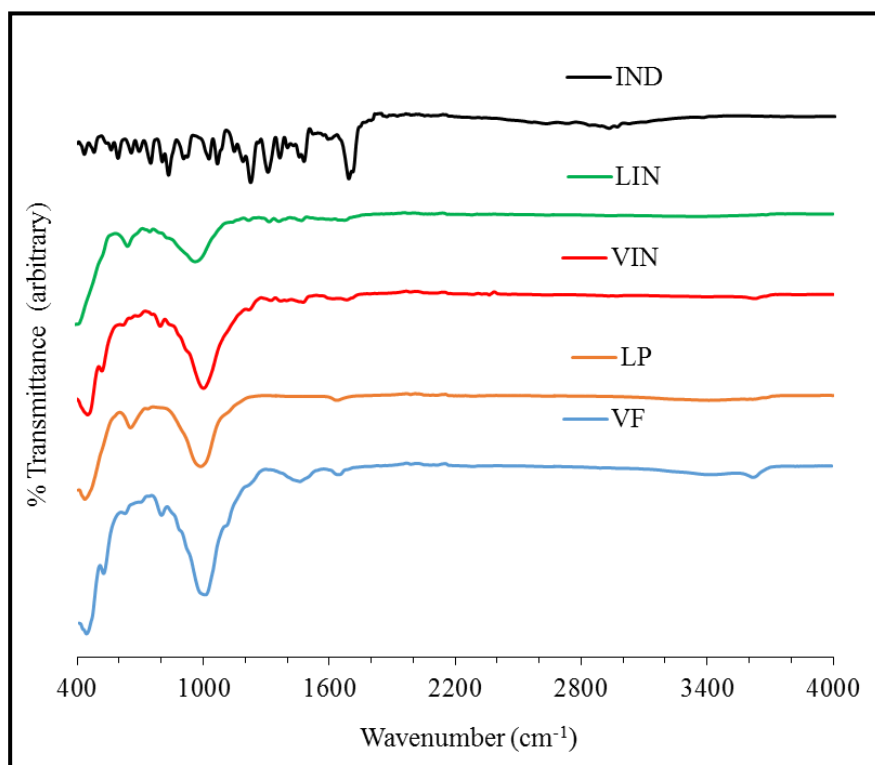
of drug or polymeric blends (29,30).

243

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245 **ATR- FTIR spectroscopic analysis**

246 ATR-FTIR spectra of pure drug, clays and drug-clay complexes are shown in Fig. 5. Both VF  
247 and LP clays showed a broad band at  $3400\text{ cm}^{-1}$  due to  $-\text{OH}$  stretching band for interlayer  
248 adsorbed water (31). The band around  $3640$  and  $3690\text{ cm}^{-1}$  is due to the  $\text{Al-OH}$  and  $\text{Si-OH}$   
249 stretching respectively (32). The presence of several hydroxyl groups in the clay contributes to  
250 the broadness of this stretching band. The absorption peak at  $1650\text{ cm}^{-1}$  belongs to the bending  
251 mode of hydroxyl group of the interlayer water molecules.



252

253 **Fig. 5.** ATR-FTIR spectrum of pure IND, VF, LP and VIN, LIN extruded formulations.

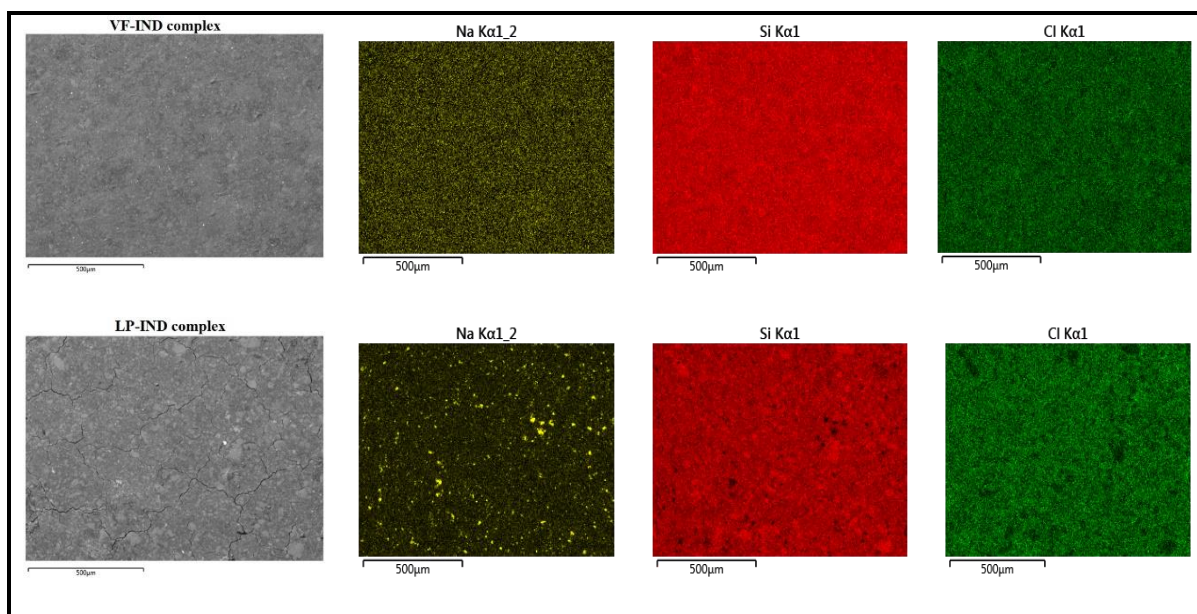
254 The characteristic peak at  $1000\text{ cm}^{-1}$  is related to the  $\text{Si-O}$  stretching vibration of the clay  
255 (33,34). IND spectra showed  $\text{C=O}$  stretching vibration in the range of  $1600\text{-}1750\text{ cm}^{-1}$  while  
256 the peak at  $1694\text{ cm}^{-1}$  is the characteristic of polymorphic Form – I of the drug substance (35).  
257 IND presents also a carbonyl and benzoyl groups at  $1694\text{ cm}^{-1}$  and  $1688\text{ cm}^{-1}$  respectively.  
258 Extruded VIN and LIN formulations showed that stretching vibration of IND at  $1694\text{ cm}^{-1}$  was

259 shifted to around  $1670\text{ cm}^{-1}$  which indicates that crystalline structure of IND has transformed  
260 to the amorphous state (36,37). The changes in the carbonyl spectral region indicate an  
261 alteration in the drug's molecular state where the shifting of carbonyl stretching is attributed to  
262 the disruption of IND-IND molecular interactions in its crystal structure. The bonding energy  
263 of carbonyl oxygen from IND decreases after adsorption of the drug onto the clay silicate,  
264 resulting a weakening of the carbonyl peak at  $1670\text{ cm}^{-1}$ . Finally, the shift of the carbonyl band  
265 suggests possible H-bonding formation with the clay platelets (35).

### 266 **EDX spectroscopic analysis**

267 Microscopic analysis and elemental mapping were studied for the drug-clay solid dispersions  
268 to evaluate the presence and distribution of IND in the clay matrices. As shown in Fig. 6,  
269 micrographs were collected using back-scattered electrons and corresponding EDX elemental  
270 maps of Na, Si and Cl showing variation of clay and drug distribution within the extruded  
271 samples. Clays such as VF primarily contain Na, Mg, Ca, Si and LP contains Na, Mg, Li, Si  
272 atoms in its structure (38,39). Heavier elements in a molecule appears brighter in a  
273 backscattered electron micrograph compared to the lighter atoms. The above micrographs in  
274 grayscale clearly explains the homogeneous distribution of VF and agglomerated LP clay  
275 distribution in the VIN and LIN dispersions respectively. X-ray elemental mapping of Na and  
276 Si (presented in yellow and red respectively, top) also confirmed homogenous distribution of  
277 VF in the VIN complex. In contrast, LIN extrudates exhibited a more inhomogeneous  
278 dispersion with areas high in Na and P (P EDX map not shown) indicating an additional phase  
279 in the drug-clay matrix (shown in the Na and Si ion map, bottom).





280 **Fig. 6.** Elemental analysis of extruded formulations, collected using SEM (Top – BSE  
 281 micrograph of VIN extrudates and its Na, Si, Cl mapping; Bottom – BSE micrograph of LIN  
 282 extrudates and its Na, Si, Cl mapping)

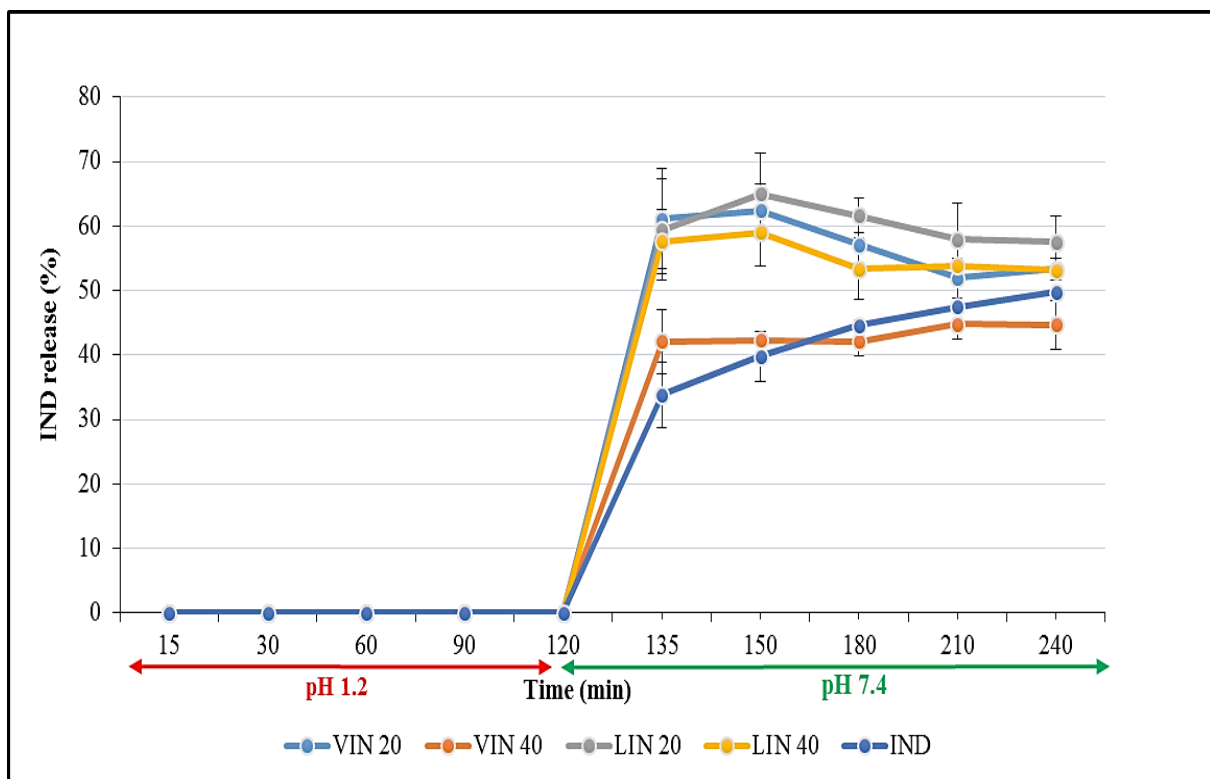
283 Furthermore, chemical structure of IND contains chlorine (Cl) atom in its chemical structure  
 284 while both the clays have no Cl present. Therefore, an X-ray elemental mapping of Cl as a  
 285 marker will reveal the homogeneity of drug distribution. Mapping data of Cl (presented in green)  
 286 shows that VIN extrudate contains uniform drug distribution where else LIN complex shows  
 287 presence of dark area, indicating a less uniform clay drug distribution. These type of poly-  
 288 dispersions may be minimised by optimising the processing parameters during extrusion.

### 289 ***In-vitro* dissolution study**

290 The *in-vitro* dissolution study was conducted using extruded drug-clay complex formulations  
 291 and the bulk drug substance. The results of the study are shown in Fig. 7. The use of smectite  
 292 clays for the development of amorphous solid dispersions facilitated controlled release of the  
 293 drug substance for both formulations. As shown in Fig. 7, dissolution studies presented a lag  
 294 time with no IND release in acidic (pH 1.2) dissolution media. After 120 min, the pH was

295 adjusted to 7.4 and bulk IND presented 33% and 50% drug release at 15 min and 120 min  
296 respectively.

297 In contrast, clay-drug complexes showed a burst release of IND from the clay matrices at 135  
298 min. The VIN 20 and LIN 20 solid dispersions showed almost 60% drug release within the first  
299 15 min. At higher drug loadings, LIN 40 also presented rapid dissolution rates at 57% while  
300 the VIN 40 at 47% respectively. This could be attributed to the higher particle size of VIN 40  
301 and LIN 40 formulations.



302

303 **Fig. 7.** *In-vitro* dissolution profiles of pure IND and HME extruded formulations at pH 1.2 (0-120  
304 min) and pH 7.4 (120-240 min).

305 Overall, the increase of dissolution rates could be attributed to several factors such as the  
306 amorphous form of IND molecules, particle size and H-bonding due to the drug-clay  
307 interactions. The clay particles may have shown some ionic interactions between adsorbate  
308 and adsorbent surface during the release study at pH 7.4 (40,41). As IND is a weak acid, the

309 highly negative surface charge of the clay at pH 7.4, might have induced dissociation of IND  
310 molecule resulting in burst release. In addition, the negatively charged smectite particles  
311 (negative charges on the border plane of the smectite layers) may have also created repulsive  
312 forces to IND that led to drug desorption from the clay matrices (42,43).

313 Although, a burst release of IND was initially observed, it can be seen in Fig. 7 that IND  
314 dissolution rates decreased over time. This can be attribute to possible IND recrystallisation  
315 where the amorphous drug crystallized in the dissolution media due to the generated  
316 supersaturation solution (25,44). Nevertheless, it can be concluded that the dissolution rate  
317 improvement of IND was achieved not only by conversion of its physical form but also through  
318 the specific chemical environment created by clay silicates.

## 319 CONCLUSIONS

320 The current study about smectite clays were introduced as an alternative drug carrier for the  
321 formation of IND amorphous solid dispersions. PXRD and DSC studies demonstrated that  
322 IND was converted into amorphous form while EDX analysis revealed excellent IND content  
323 uniformity in the clay matrices due to extrusion processing. The extruded ASD presented  
324 controlled release with rapid IND dissolution rates in alkaline media for drug loadings varying  
325 from 20 to 40%. In conclusion, smectite clays can be used as a drug carriers for the  
326 development of ASDs at up to 40% high drug loadings.

## 327 DISCLOSURE STATEMENT

328 The authors report no conflict of interests.

## 329 ACKNOWLEDGEMENTS

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332 **REFERENCES**

- 333 1. Keserü GM, Makara GM. The influence of lead discovery strategies on the properties  
334 of drug candidates. *Nat Rev Drug Discov.* 2009;8(3):203–12.
- 335 2. Lipinski CA. Drug-like properties and the causes of poor solubility and poor  
336 permeability. *J Pharmacol Toxicol Methods.* 2000;44(1):235–49.
- 337 3. Hiendrawan S, Widjojokusumo E, Veriansyah B, Tjandrawinata RR. Pharmaceutical  
338 salts of carvedilol: polymorphism and physicochemical properties. *AAPS*  
339 *PharmSciTech.* 2017;18(4):1417–25.
- 340 4. Box KJ, Comer J, Taylor R, Karki S, Ruiz R, Price R, et al. Small-scale assays for  
341 studying dissolution of pharmaceutical cocrystals for oral administration. *AAPS*  
342 *PharmSciTech.* 2016;17(2):245–51.
- 343 5. Upadhye SB, Kulkarni SJ, Majumdar S, Avery MA, Gul W, ElSohly MA, et al.  
344 Preparation and Characterization of Inclusion Complexes of a Hemisuccinate Ester  
345 Prodrug of  $\Delta$  9-Tetrahydrocannabinol with Modified Beta-Cyclodextrins. *Aaps*  
346 *Pharmscitech.* 2010;11(2):509–17.
- 347 6. Wang L, Li H, Wang S, Liu R, Wu Z, Wang C, et al. Enhancing the antitumor activity  
348 of berberine hydrochloride by solid lipid nanoparticle encapsulation. *Aaps*  
349 *Pharmscitech.* 2014;15(4):834–44.
- 350 7. Haser A, Zhang F. New strategies for improving the development and performance of  
351 amorphous solid dispersions. *Aaps Pharmscitech.* 2018;19(3):978–90.
- 352 8. Sekiguchi K, Obi N. Studies on Absorption of Eutectic Mixture. I. A Comparison of the  
353 Behavior of Eutectic Mixture of Sulfathiazole and that of Ordinary Sulfathiazole in Man.  
354 *Chem Pharm Bull.* 1961;9(11):866–72.

- 355 9. Abend S, Lagaly G. Sol–gel transitions of sodium montmorillonite dispersions. Appl  
356 Clay Sci. 2000;16(3–4):201–27.
- 357 10. Carretero MI, Pozo M. Clay and non-clay minerals in the pharmaceutical industry Part  
358 I. Excipients and medical applications. Appl Clay Sci. 2009;46:73–80.
- 359 11. Viseras C, Lopez-Galindo A. Pharmaceutical applications of some Spanish clays  
360 (sepiolite, palygorskite, bentonite): some preformulation studies. Appl Clay Sci.  
361 1999;14(1–3):69–82.
- 362 12. Carretero MI, Pozo M. Clay and non-clay minerals in the pharmaceutical industry. Part  
363 I. Excipients and medical applications. Appl Clay Sci. 2009;46(1):73–80.
- 364 13. Adebisi AO, Conway BR, Asare-Addo K. The influence of fillers on theophylline  
365 release from clay matrices. Am J Pharmacol Sci. 2015;3(5):120–5.
- 366 14. Gonçalves MLCM, Lyra MAM, Oliveira FJVE, Rolim LA, Nadvorny D, Vilarinho  
367 ACSG, et al. Use of phyllosilicate clay mineral to increase solubility olanzapine. J  
368 Therm Anal Calorim. 2017;127(2):1743–50.
- 369 15. Adebisi AO, Conway BR, Asare-Addo K. The influence of fillers on theophylline  
370 release from clay matrices. Am J Pharmacol Sci. 2015; 2016:120–5.
- 371 16. Kim MH, Choi G, Elzatahry A, Vinu A, Choy Y Bin, Choy JH. Review of clay-drug  
372 hybrid materials for biomedical applications: Administration routes. Clays Clay Miner.  
373 2016;64(2):115–30.
- 374 17. McPhee C, Reed J, Zubizarreta I. Core Sample Preparation. In: Developments in  
375 Petroleum Science. Elsevier; 2015. p. 135–79.
- 376 18. Jung H, Kim H, Bin Y, Hwang S, Choy J. Laponite-based nanohybrid for enhanced  
377 solubility and controlled release of itraconazole. Int J Pharm. 2008;349:283–90.

- 378 19. Bahl D, Hudak J, Bogner RH. Comparison of the ability of various pharmaceutical  
379 silicates to amorphize and enhance dissolution of indomethacin upon co-grinding.  
380 Pharm Dev Technol. 2008;13(3):255–69.
- 381 20. Löbenberg R, Amidon GL. Modern bioavailability, bioequivalence and  
382 biopharmaceutics classification system. New scientific approaches to international  
383 regulatory standards. Eur J Pharm Biopharm. 2000;50(1):3–12.
- 384 21. Alsaidan SM, Alsughayer AA, Eshra AG. Improved Dissolution Rate of Indomethacin  
385 by Adsorbents. Drug Dev Ind Pharm [Internet]. 1998 Jan 1;24(4):389–94.
- 386 22. Zhang W, Zhang C ning, He Y, Duan B yan, Yang G yi, Ma W dong, et al. Factors  
387 Affecting the Dissolution of Indomethacin Solid Dispersions. AAPS PharmSciTech.  
388 2017;18(8):3258–73.
- 389 23. Hwang I, Kang C-Y, Park J-B. Advances in hot-melt extrusion technology toward  
390 pharmaceutical objectives. J Pharm Investig. 2017;47(2):123–32.
- 391 24. Prasad D, Chauhan H, Atef E. Amorphous stabilization and dissolution enhancement of  
392 amorphous ternary solid dispersions: combination of polymers showing drug–polymer  
393 interaction for synergistic effects. J Pharm Sci. 2014;103(11):3511–23.
- 394 25. Maniruzzaman M, Nair A, Scoutaris N, Bradley MSA, Snowden MJ, Douroumis D.  
395 One-step continuous extrusion process for the manufacturing of solid dispersions. Int J  
396 Pharm. 2015;496(1):42–51.
- 397 26. Villar M V, Gómez-Espina R, Gutiérrez-Nebot L. Basal spacings of smectite in  
398 compacted bentonite. Appl Clay Sci. 2012;65:95–105.
- 399 27. El-Badry M, Fetih G, Fathy M. Improvement of solubility and dissolution rate of  
400 indomethacin by solid dispersions in Gelucire 50/13 and PEG4000. Saudi Pharm J.

- 401 2009;17(3):217–25.
- 402 28. Grim RE, Bradley WF. Investigation of the effect of heat on the clay minerals illite and  
403 montmorillonite. *J Am Ceram Soc.* 1940;23(8):242–8.
- 404 29. Corcione CE, Maffezzoli A. *Thermochimica Acta* Glass transition in thermosetting clay-  
405 nanocomposite polyurethanes. 2009;485:43–8.
- 406 30. Qazvini NT, Chehrazi E. Glass transition behavior and dynamic fragility of PMMA-  
407 SAN miscible blend-clay nanocomposites. *J Macromol Sci Part B Phys.*  
408 2011;50(11):2165–77.
- 409 31. Tabak A, Yilmaz N, Eren E, Caglar B, Afsin B, Sarihan A. Structural analysis of  
410 naproxen-intercalated bentonite (Unye). *Chem Eng J.* 2011;174(1):281–8.
- 411 32. Kevadiya BD, Patel HA, Joshi G V, Abdi SHR, Bajaj HC. Montmorillonite-Alginate  
412 Composites as a Drug delivery System : Intercalation and In vitro Release of Diclofenac  
413 sodium. *Indi.* 2010;72(6):732–7.
- 414 33. Patel HA, Somani RS, Bajaj HC, Jasra R V. Preparation and characterization of  
415 phosphonium montmorillonite with enhanced thermal stability. *Appl Clay Sci.*  
416 2007;35(3–4):194–200.
- 417 34. Ghadiri M, Chrzanowski W, Lee WH, Fathi A, Dehghani F, Rohanizadeh R. Physico-  
418 chemical, mechanical and cytotoxicity characterizations of Laponite®/alginate  
419 nanocomposite. *Appl Clay Sci.* 2013;85:64–73.
- 420 35. A RM, Kebriaee A, Keshavarz M, Ahmadi A, Mohtat B. Preparation and in-vitro  
421 evaluation of indomethacin nanoparticles. 2010;18(3):185–92.
- 422 36. Fini A, Cavallari C, Ospitali F. Raman and thermal analysis of indomethacin/PVP solid  
423 dispersion enteric microparticles. *Eur J Pharm Biopharm.* 2008;70(1):409–20.

- 424 37. Kocbek P, Baumgartner S, Kristl J. Preparation and evaluation of nanosuspensions for  
425 enhancing the dissolution of poorly soluble drugs. *Int J Pharm.* 2006;312(1–2):179–86.
- 426 38. Jatav S, Joshi, M Y. Chemical stability of Laponite in aqueous media. *Appl Clay Sci.*  
427 2014;97–98(August):72–7.
- 428 39. Trivedi V, Nandi U, Maniruzzaman M, Coleman NJ. Intercalated theophylline-smectite  
429 hybrid for pH-mediated delivery. *Drug Deliv Transl Res.* 2018;8:1781–9.
- 430 40. Netpradit S, Thiravetyan P, Towprayoon S. Adsorption of three azo reactive dyes by  
431 metal hydroxide sludge: effect of temperature, pH, and electrolytes. *J Colloid Interface*  
432 *Sci.* 2004;270(2):255–61.
- 433 41. Tabak A, Eren E, Afsin B, Caglar B. Determination of adsorptive properties of a Turkish  
434 Sepiolite for removal of Reactive Blue 15 anionic dye from aqueous solutions. *J Hazard*  
435 *Mater.* 2009;161(2–3):1087–94.
- 436 42. Tabak A, Baltas N, Afsin B, Emirik M, Caglar B, Eren E. Adsorption of Reactive Red  
437 120 from aqueous solutions by cetylpyridinium-bentonite. *J Chem Technol Biotechnol.*  
438 2010;85(9):1199–207.
- 439 43. Tombacz E, Szekeres M. Colloidal behavior of aqueous montmorillonite suspensions:  
440 the specific role of pH in the presence of indifferent electrolytes. *Appl Clay Sci.*  
441 2004;27(1–2):75–94.
- 442 44. Alonzo DE, Zhang GGZ, Zhou D, Gao Y, Taylor LS. Understanding the behavior of  
443 amorphous pharmaceutical systems during dissolution. *Pharm Res.* 2010;27(4):608–18.
- 444
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