Drug – smectite clay amorphous solid dispersions processed by Hot Melt Extrusion

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Abstract

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

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

INTRODUCTION

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

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

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

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

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

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

MATERIALS AND METHODS

Materials

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

Continuous possessing of ASD using HME

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

Table I. Formulations used for continuous solid dispersion using HME

Formulation	IND (%)	VF (%)	LP (%)
VIN-20	20.0	80.0	-

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

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

Fig. 1. Photograph of screw configuration.

Morphology analysis of extrudates

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

PXRD analysis

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

prepared using a PMMA (Poly-methyl-methacrylate) sample holder which was scanned from 2 to 56 º2θ with a step size 0.02 º2θ, counting time 0.1 s per step and a rotation of 15 rpm.

DSC analysis

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

ATR-FTIR analysis

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

EDX analysis

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

***In-vitro* dissolution study**

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

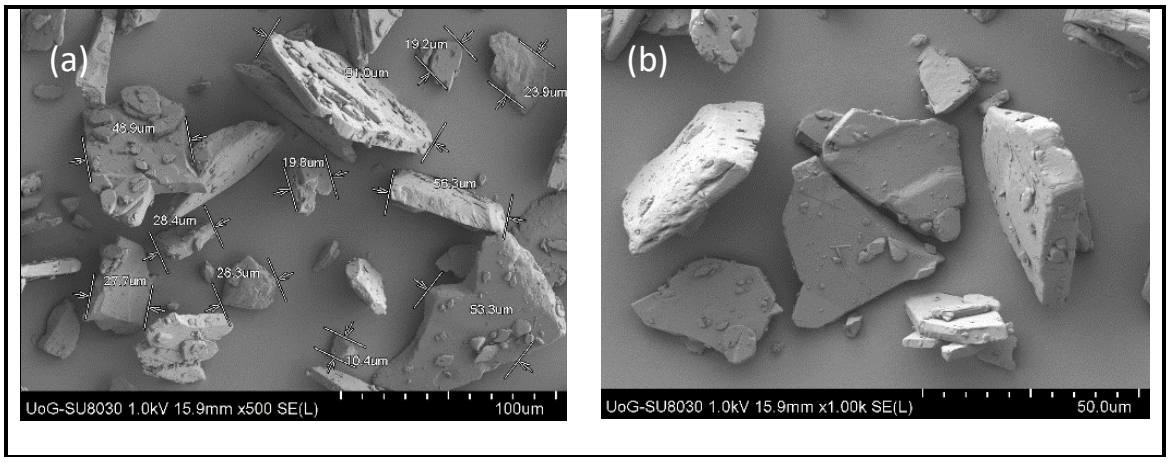
pH was adjusted to 7.4 using NaOH solution. Samples were collected at 15, 30, 60, 90, 120 min time interval from both pH and dissolution studies were also performed in triplicate. Samples were then analysed using a high performance liquid chromatographic system provided by Agilent Technologies, 1200 series (USA). IND was analysed using a HYCHROME S5ODS2-4889 (5×150×4 mm) column and an UV detector at a wavelength of 214 nm. The mobile phase were prepared using acetonitrile: water: Ortho-phosphoric acid (49.5: 49.3: 0.2 v/v) and pumped at a flow rate of 1.5 mL/min. Abovementioned specification showed a 112 to 114 bar of column back pressure with a retention time of 3.00 ± 0.1 min. Calibration curve was also prepared using 20, 40, 60, 80 and 100 µg/mL concentrated ethanolic solution of IND.

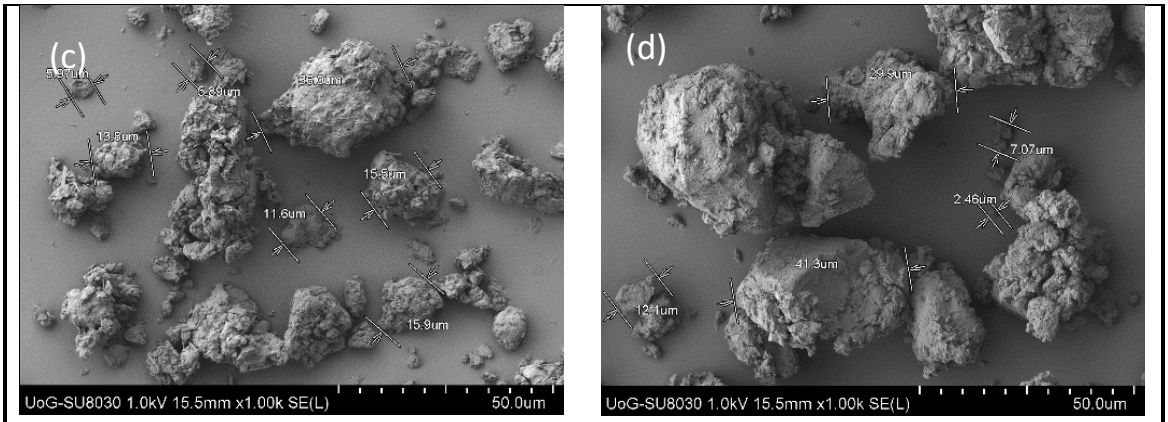
RESULTS AND DISCUSSIONS

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

Morphology analysis of extrudates

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

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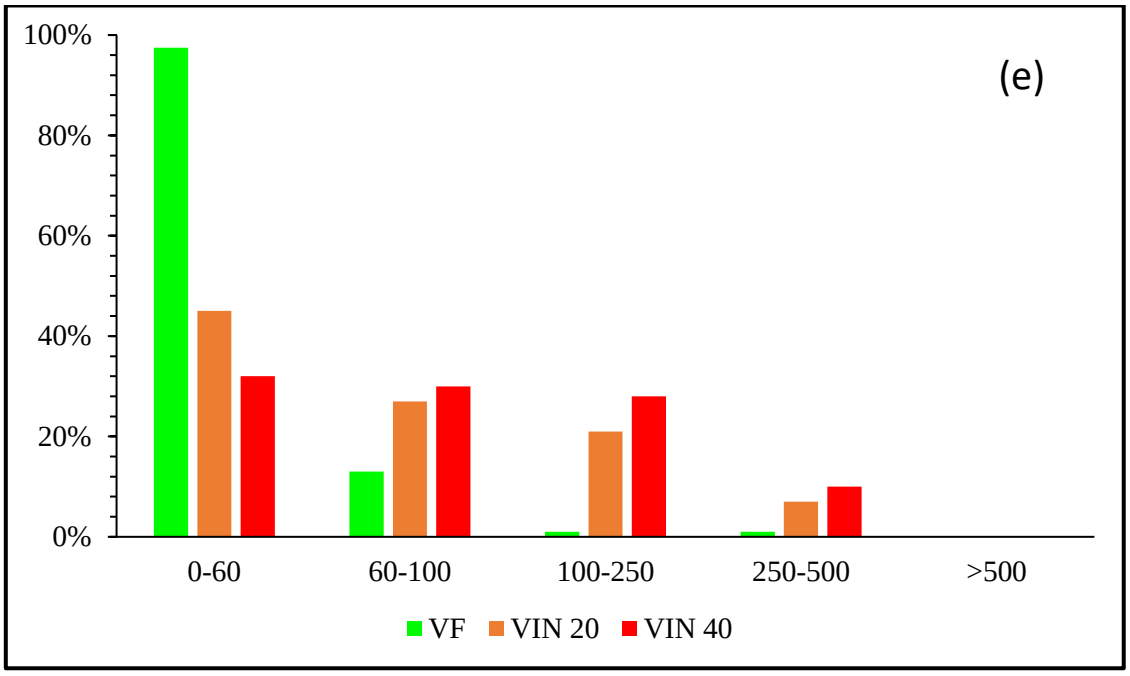
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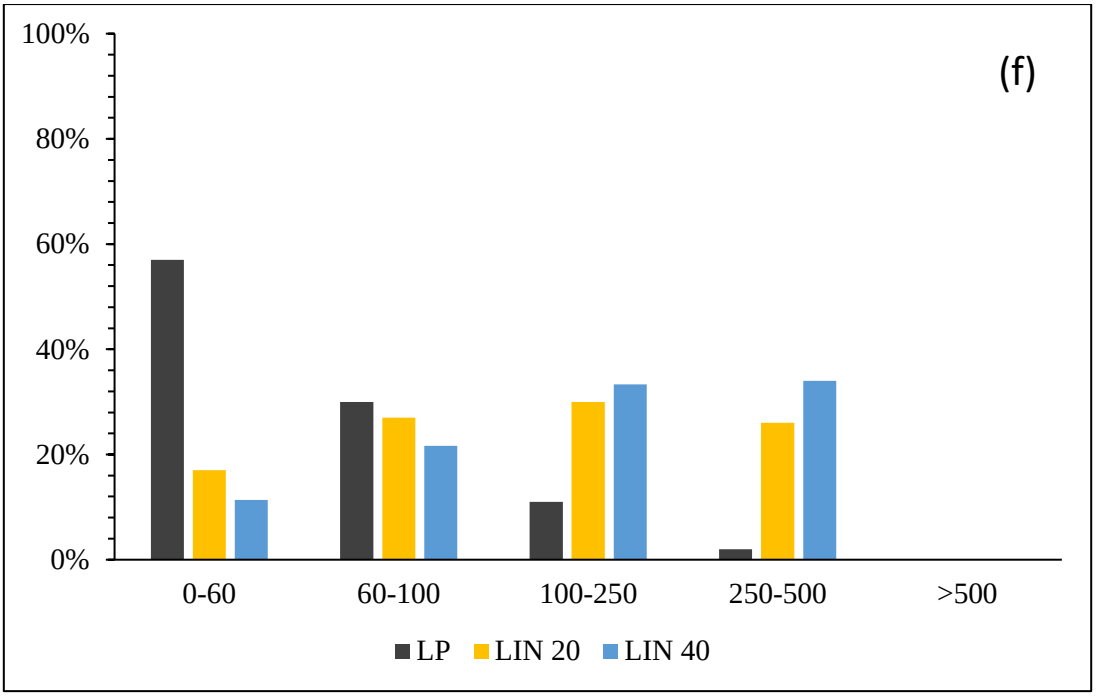

Fig. 2. (Top) SEM micrographs of (a-b) pure IND, c- VIN and d- LIN extruded formulations. (Bottom) Particle size distribution of VIN, LIN extruded formulations against pure clay.

PXRD analysis

The physical state of the crystalline drug, clay and their extruded formulations were examined using PXRD analytical technique and shown in Fig. 3. Diffractogram of crystalline IND showed peaks with sharp intensity at 9.1, 10.6, 11.7, 15.8, 18.6, 20.8, 25.6 and 28.3 º2θ. Pure clays, VF and LP also showed their primary peaks at 7.4, 19.9, 21.9 º2θ and 6.5, 20.1, 33.3 º2θ respectively. Interlayer spacing for pure VF at 7.4 º2θ= 11.9 Å and LP at 6.5 º2θ= 13.6 Å was found using Bragg's law ($n\lambda=2d\sin\theta$). Although the interlayer spacing of anhydrous smectite clay should be ~ 10 Å, presence of homogeneous water molecules increases the interlayer spacing between two aluminosilicate sheets (26). The broad interlayer spacing also indicates the poor organisation of silicate layers in the structure. PXRD pattern of VIN and LIN formulations showed higher basal spacing compare to the pure clays. In particular, the basal spacing of VIN was indistinguishable in obtained the diffractogram. The IND – VIN and IND – LIN extruded formulation did not present any intensity peaks related to bulk IND. These

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

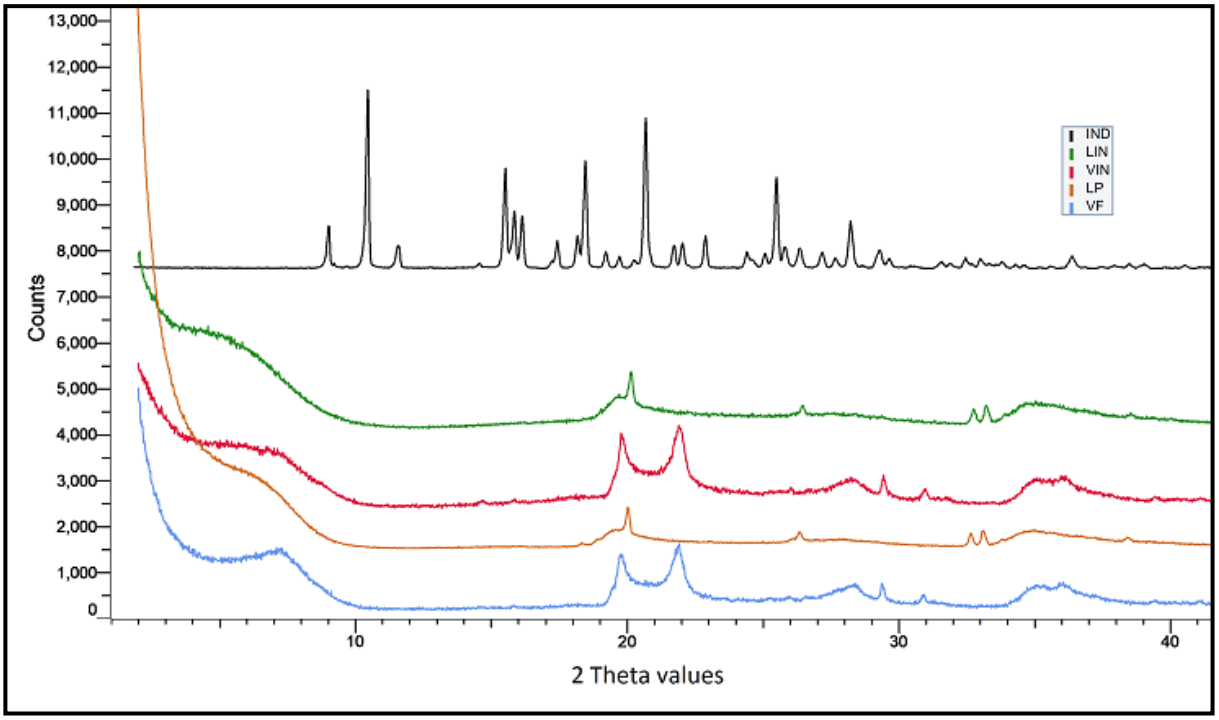

Fig. 3. PXRD diffractograms of bulk IND, smectite clays and extruded formulations.

DSC analysis

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

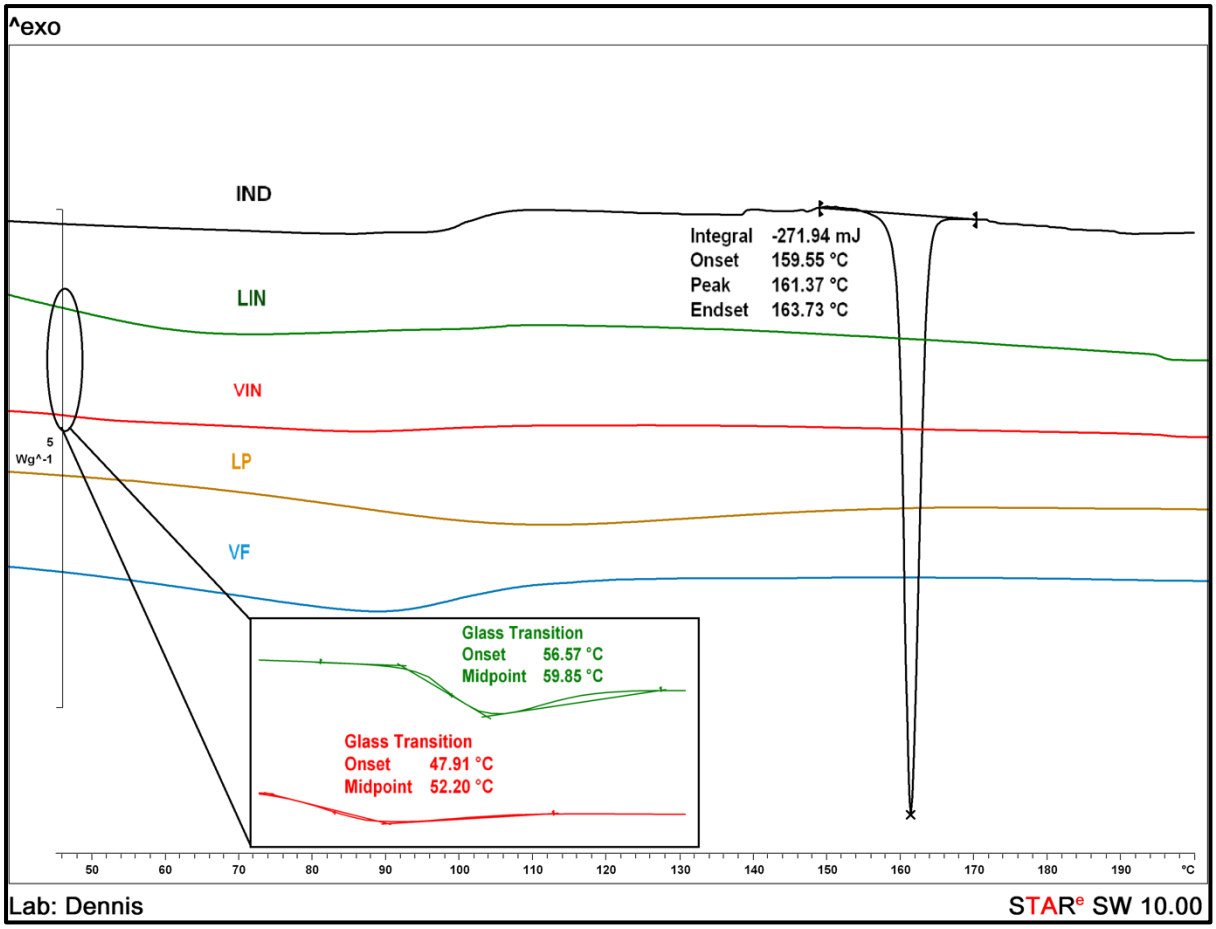

Fig. 4. Thermal transitions of pure IND, VF, LP, VIN and LIN extruded formulations.

Similarly, thermograms of VIN and LIN extruded formulations presented water loss at 30-110 ºC with lower enthalpy values due to the HME processing at 170 ºC. Fig. 4 also shows that the absence of IND melting endothermic peak in VIN and LIN formulations (22,27). Most importantly, the VIN and LIN thermograms presented endothermic events at 47.91 and 56.57 ºC respectively which might correspond to the drug's T_g where for the amorphous IND is around at 46 ºC. However, the observed endothermic events showed a shift of T_g to higher temperatures which is not unusual and it has been reported that clays can shift glass transitions of drug or polymeric blends (29,30).

ATR- FTIR spectroscopic analysis

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

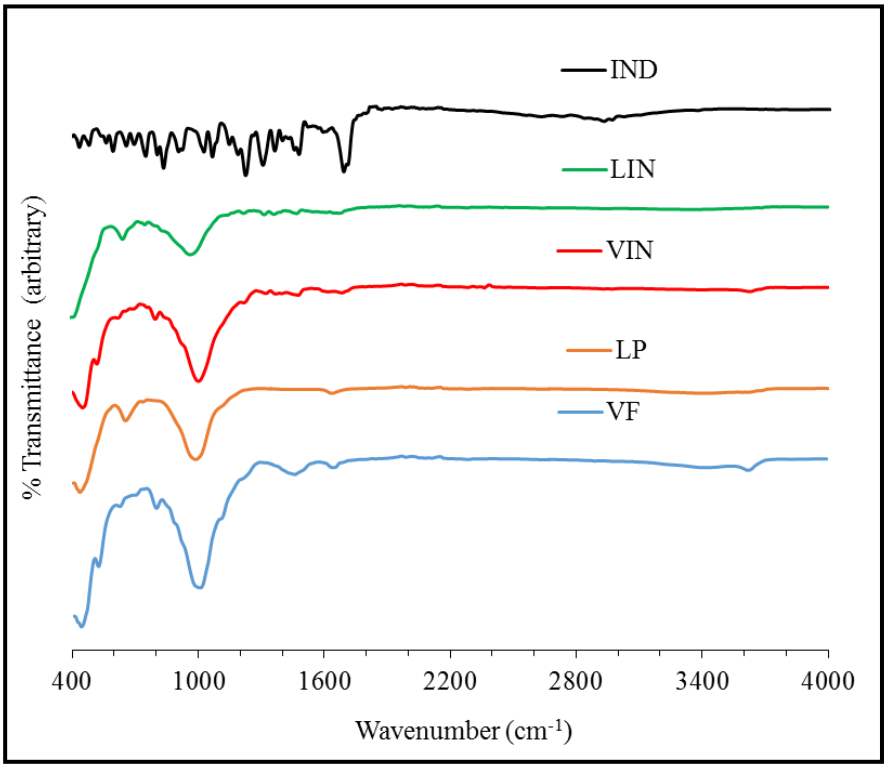

Fig. 5. ATR-FTIR spectrum of pure IND, VF, LP and VIN, LIN extruded formulations.

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

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

EDX spectroscopic analysis

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

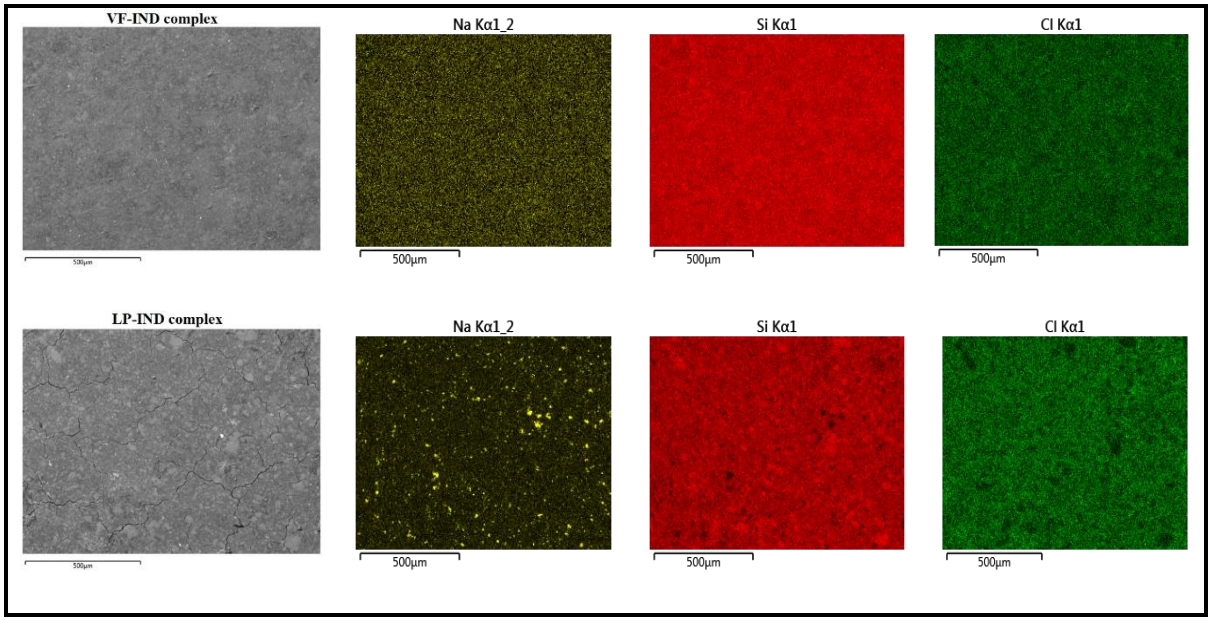

Fig. 6. Elemental analysis of extruded formulations, collected using SEM (Top – BSE micrograph of VIN extrudates and its Na, Si, Cl mapping; Bottom – BSE micrograph of LIN extrudates and its Na, Si, Cl mapping)

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

In-vitro dissolution study

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

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

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

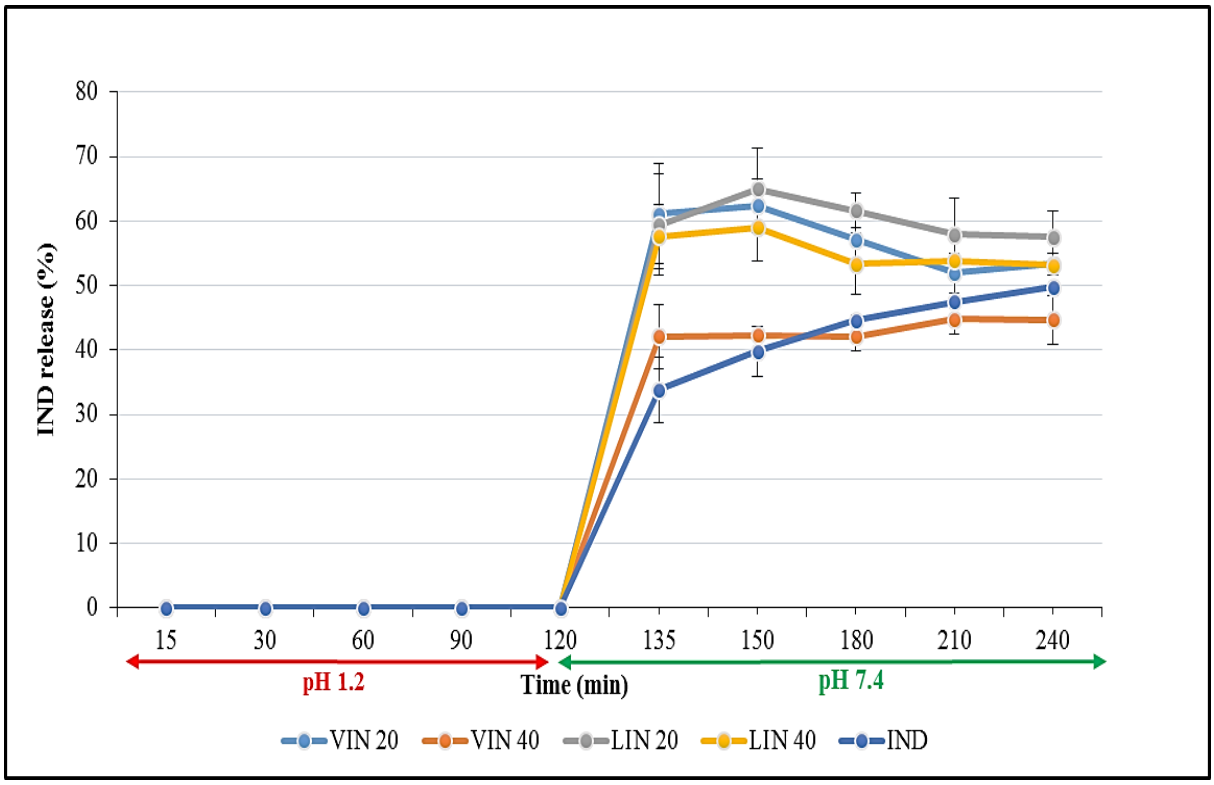

Fig. 7. *In-vitro* dissolution profiles of pure IND and HME extruded formulations at pH 1.2 (0-120 min) and pH 7.4 (120-240 min).

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

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

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

CONCLUSIONS

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

DISCLOSURE STATEMENT

The authors report no conflict of interests.

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