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Mesoporous Silica-Based Strategy for Enhancing Indomethacin Dissolution: Syloid® XDP 3050 for Oral Equine Delivery

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Mesoporous silica excipient Syloid® XDP 3050 was formulated with indomethacin, a model drug characterised by poor aqueous solubility, to enhance its dissolution rate and extent. While various mesoporous silicas have been previously studied, the specific interaction and performance of Syloid® XDP 3050 with indomethacin had not been reported. Formulations at drug-to-silica ratios of 1:1, 2:1, and 1:3 (w/w) were prepared using the microwave method and characterised by DSC, XRD, FTIR, and SEM. *In vitro* dissolution was assessed in phosphate buffer (pH 7.0) at 37 °C for 45 min using the USP type II paddle method. This study demonstrates a significant improvement in both the dissolution rate and extent of drug release at drug-to-silica ratios of 1:1, 2:1, and 1:3 over 45 minutes. DSC and XRD confirmed the conversion of indomethacin from crystalline to amorphous form in all microwave-processed formulations. FTIR revealed no evidence of strong chemical interactions, while SEM images showed the drug uniformly dispersed within the silica matrix. The observed enhancement is attributed to the conversion of indomethacin from its crystalline to amorphous form, as well as the silica's superior drug-loading capacity within its porous structure. Variations in release profiles among the different ratios were linked to the physicochemical properties of the formulations. Overall, the findings confirm that Syloid® XDP 3050 can effectively enhance the dissolution and potentially the bioavailability of poorly water-soluble drugs like indomethacin. Moreover, drug release profiles can be modulated by selecting appropriate silica types and drug-to-carrier ratios, offering a promising approach to tailor oral drug delivery systems.

Keywords: Mesoporous silica, Syloid® XDP 3050, Indomethacin, Oral drug delivery, Drug loading.

1. Introduction

Mesoporous silica materials have gained considerable attention as carriers for the oral delivery of poorly water-soluble drugs since their initial development in the 1970s. These materials are characterised by pore diameters ranging from 2 to 50 nm, hence the term *"mesoporous"* with an ordered arrangement of uniform pores embedded within an amorphous silica matrix [1]. Key advantages of mesoporous silicas include their high surface area, large pore volume, tunable pore and particle size, flexible morphology, excellent biocompatibility, ease of surface functionalization, and biodegradability [2]. Owing to these properties, they have been widely applied in drug delivery systems, catalysis, adsorption, environmental remediation, and chromatography [3–5].

A significant number of drug candidates exhibit poor aqueous solubility, which poses major challenges in formulation development and often results in suboptimal bioavailability or the rejection of promising compounds during early stages of drug development [6]. Enhancing the solubility and dissolution rate of such drugs—without compromising their chemical stability or pharmacological efficacy—remains a persistent challenge in pharmaceutical formulation science. Various conventional and advanced strategies have been employed to address this issue, including the use of gelatin and non-gelatin capsules [7], co-solvents, solid dispersions, salt formation, lipid-based systems [8,9], mesoporous carriers [10,11], liposomes [12], inclusion complexes (e.g., cyclodextrins) [13], polymer-based formulations [14], and nanocarrier-based delivery platforms [15]. These approaches have contributed to improved drug release profiles, enhanced bioavailability, reduced dosing frequency, and better patient compliance. Nonetheless, a subset of poorly soluble drugs continues to present significant formulation

challenges, necessitating further innovation in drug delivery technologies.

Among the various formulation strategies, mesoporous silica-based carriers have shown promising potential due to their unique structural and physicochemical features. A particularly underexplored class of mesoporous silica materials is the Syloid® XDP 3050. This silica possesses a highly developed porous network, combining high adsorption capacity with favourable pore size distribution and surface morphology. Traditionally, Syloid® silicas have been employed to improve the flowability of powders and convert liquid APIs into free-flowing powders. However, their potential in enhancing drug dissolution has received limited attention. To date, only two forms—Syloid® 244 and AL-1 FP—have been evaluated in combination with model drugs such as indomethacin [16-17] and itraconazole [18], both showing improvements in dissolution rate and extent. Despite these promising findings, other Syloid® variants such as XDP 3050 remain largely uninvestigated, even though they may offer additional advantages for drug loading and controlled release.

Therefore, the present study investigates the ability of Syloid® XDP 3050 to enhance the dissolution profile of indomethacin—a non-steroidal anti-inflammatory drug (NSAID) with known solubility limitations—using different drug-to-silica ratios. This study aims to assess the effect of the carrier on the rate and extent of drug release and to provide mechanistic insights into the drug–silica interactions responsible for any observed enhancement.

2. Materials and Methods

2.1. Materials

Indomethacin, potassium phosphate dibasic, and potassium phosphate monobasic (all ≥ 99%) were purchased from Sigma Aldrich (Dorset, UK) and used as received. Syloid silica XDP 3050 was kindly donated by Glantreo Ltd, Cork, Ireland and W. R. Grace & Co, Maryland, USA. Table 1 provides a summary of the physicochemical properties of the Syloid silica, and the data presented were determined using nitrogen gas sorption isotherms. These measurements were taken at 77 K using a Micromeritics TriStar II surface area analyser (Micromeritics, Norcross, GA, USA). Samples were pre-treated by heating at 200°C under nitrogen for 12 hours. The surface area was measured using the Brunauer-Emmett-Teller (BET) method. The pore volume and pore diameter data were calculated using the Barrett, Joyner and Halenda (BJH) method [2].

Table 2. 1: The physicochemical properties of the Syloid® silicas used in this study [11, 15].

Name	Average Particle Size (μm)	Shape	Surface Area (m2g-1)	Pore Volume (cm^3g^{-1})	Pore Diameter (Å)
Syloid XDP 3050	48 – 66	Irregular	320	1.70	229

2.2 Methods

2.2.1 Microwave formulation

A known mass (30 - 80 mg) of the physically mixed indomethacin with Syloid XDP 3050 at 1:1, 2:1 and 1:3 drug-to-excipient mass ratios was transferred into a quartz crucible and placed in the microwave. The microwave heating system was operated and controlled by software previously published [19]. The software was set to continuously modify the microwave power such that the samples were heated at 5 ^oC/min to the melting temperature of the drug from 25 – 200 ^oC. The formulations were held isothermally for 5 min and then cooled over 60 – 80 min under an air atmosphere, utilising a microwave power of 30 to 45 W.

2.3 Solid state characterisation

2.3.1 Differential scanning calorimetry (DSC) for solid-state characterisation

Differential scanning calorimetry (DSC) was performed using a Mettler Toledo DSC 1 equipped with a chiller cooling apparatus. Samples of pure drug, physical mixtures, as well as their formulations, were scanned individually using a mass ranging from 4 to 8 mg in sealed aluminium pans heated at a rate of 10 °C/min under a nitrogen flow of 80 mL/min from 25 to 200 °C. The resultant profiles were obtained, analysed and compared.

2.3.2 X-ray diffraction (XRD)

Powder X-ray diffraction data were collected on a Bruker D_2-Phaser instrument equipped with a Cu $K\alpha_1$ radiation source at 30 kV and 10 mA current at a scanning range of 5 – 100 for 4 min. The drug and Syloid XDP 3050 were scanned individually,

followed by their physical mixtures and formulations. Diffraction patterns were obtained and compared.

2.3.3 Fourier transform infrared (FT-IR)

For stability, functional group identification, drug-drug, and drug-excipient bonding information, a Nicolet-380 Fourier Transform Infrared spectrometer (FT-IR) with an ATR crystal was used to record the infrared spectrum of the pure drug and its formulations. Powdered samples were placed directly onto the diamond crystal, and the anvil was lowered to ensure that the samples were in full contact with the diamond. Each spectrum was obtained in the range of 400 – 4000 cm^{-1} with 2 cm^{-1} resolution.

2.3.4 Scanning electron microscopy (SEM)

The morphology of the prepared samples was characterised using scanning electron microscopy (SEM), (JEOL JSM-6060LV, Japan) with gold-plating using a sputter coater (SC7620) prior to imaging. The procedure involved mounting the samples to a specimen stub and coating the surface of the material with an ultrathin layer of gold to inhibit the accumulation of electrostatic charges, making the surface of the sample electrically conductive.

2.4 *In vitro* dissolution studies

To assess drug release from the Syloid® silica formulations, dissolution analysis was carried out using the USP type II (paddle method). This was a fully automated assembly, comprising a dissolution bath (Pharmatest DT 70), peristaltic pump and UV visible spectrophotometer (Cecil 3021, series 3000). Formulated samples with a total drug content (based upon suitable calibrations using calibration data) of 21.60 mg for indomethacin were placed in 900 mL of pH 7.0 phosphate buffer, stirred at 75 rpm and at 37.0 ± 0.5 ºC, maintaining sink conditions throughout the duration of the experiment. Samples were taken by an auto-sampling system every 5 min, equipped with µm filters over a period of 45 min and returned to the original solution. The solution was measured by UV spectrophotometry (set at a wavelength (λ) of 280 for IMC) to calculate the drug concentration released using a standard calibration plot for the drug.

3. Results and Discussion

3.1. Characterisation of formulations

3.1.1 Differential scanning calorimetry (DSC)

DSC analysis was applied to investigate the phase change during the formation of solid dispersions. As reported in Figure 3.1 (a), the thermal curve of pure indomethacin was characterised by a well-defined sharp melting peak at 160.7 ºC in agreement with the melting point previously reported 158 – 162 ºC [20].

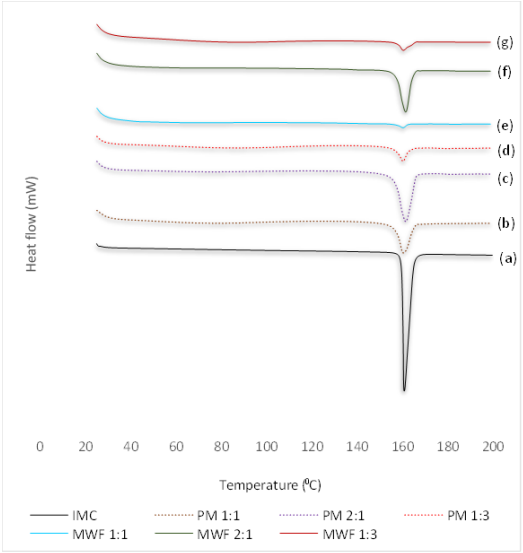

Figure 3. 1. DSC profiles for indomethacin (IMC) along XDP 3050 based physical mixtures (PM) and microwave formulations (MWF). (a) Pure IMC, (b) PM 1:1 (c) PM 2:1 (d) PM 1:3 (e) MWF 1:1 (f) MWF 2:1 and (g) MWF 1:3

In the thermal profile of physical mixtures 1:1, 2:1 and 1:3 (Figure 3.1 b, c and d), a small endothermic peak corresponding to the melting point of indomethacin was detectable; this event can be attributed to the transformation of indomethacin from crystalline to a partially amorphous form during the programmed heating. After microwave formulation, there was a reduction in the size of the drug-melting peak for the three ratios, indicating a possible dispersion of drug into Syloid® XDP 3050 carrier as a result of microwave irradiation. The drug was embedded into the Syloid® XDP 3050, thereby bringing it to a less crystalline state in agreement with the XRD data discussed below. This result is consistent with the confinement of indomethacin within mesoporous silica, as previously reported [21], where DSC thermograms typically display a reduced or absent melting endotherm, indicating drug amorphisation.

3.1.2 X-ray diffraction (XRD)

To support the results of the DSC, indomethacin, Syloid® XDP 3050, prepared physical mixtures as well as microwave formulations of the samples were analysed by XRD, and the results are presented in Figure 3.2.

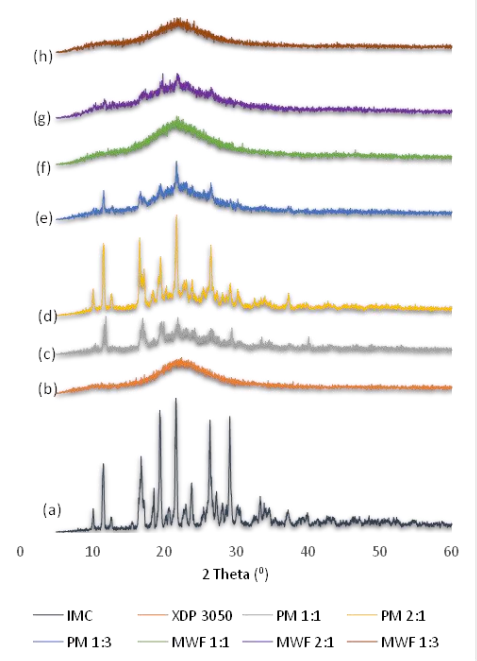

Figure 3. 2. XRD patterns for (a) IMC, (b) XDP 3050, (c) PM 1:1, (d) PM 2:1, (e) PM 1:3 (f) MWF 1:1, (g) MWF 2:1 and (h) MWF 1:3.

From the diffractions scanned, it is clear that indomethacin is a crystalline drug with high-intensity diffraction peaks, whereas the Syloid® XDP 3050 carrier is completely amorphous. Indomethacin exhibits sharp, well-defined, and high-intensity peaks in the XRD pattern, which are characteristic of a long-range ordered crystalline lattice. In contrast, the XRD pattern of Syloid® XDP 3050 shows a broad diffuse halo with no distinct diffraction peaks, a signature feature of amorphous materials that lack long-range order. The absence of sharp peaks in the Syloid® XDP 3050 profile confirms its completely amorphous nature, while the presence of intense peaks for indomethacin confirms its crystalline state. The diffractograms for the physical mixtures of indomethacin with the three Syloid® silicas at 1:1, 2:1 and 1:3 drug/silica ratios showed that the indomethacin crystalline peaks were maintained in the physical mixtures, indicating that the drug was still in a crystalline state. these results agree with the previous DSC results.

3.1.3 Fourier transform infrared spectroscopy (FT-IR)

FTIR was used to investigate the nature of the interaction taking place between the carrier Syloid® XDP 3050 and the active indomethacin. The spectrum of indomethacin, Syloid® silica, as well as their formulations, are shown in Figure 3.3.

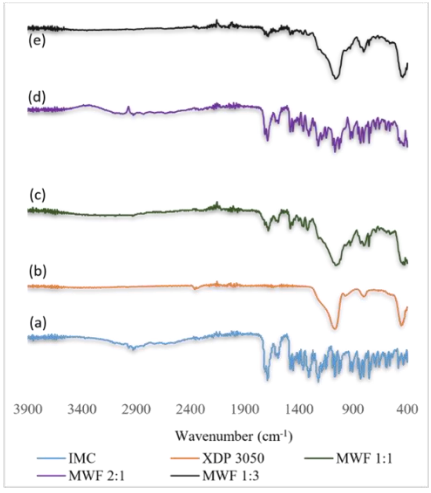

Figure 3. 3. FT-IR analysis of (a) IMC (b) XDP 3050, (c) MWF 1:1, (d) MWF 2:1, and (e) 1:3 drug-XDP 3050 formulations

The spectrum of the active drug (Figure 3.3a) showed an absorption band at 2930 cm^{-1} for hydroxyl (O-H) stretching vibrations, 1690 cm^{-1} for carbonyl (C=O), 1450 cm^{-1} for phenyl groups (C=C) and 900 cm^{-1} for the C-H vibrations of indomethacin [22]. These findings are consistent with previously reported FTIR spectra of crystalline indomethacin, where the same functional group assignments were observed, confirming the preservation of its chemical structure in the pure drug form prior to formulation.

3.1.4 Scanning electron microscopy (SEM)

An in-depth study of the morphological aspect of single-component and interacted mixtures was carried out with SEM. The findings are displayed in Figure 3.4 (x500 magnification). The drug crystalline state is evident, while the disordered, irregular shape and size of the syloid silica are also evident. Differences in images of the physical mixtures of the drug with silicas at different ratios are insignificant as confirmed by the SEM (100 µm scale).

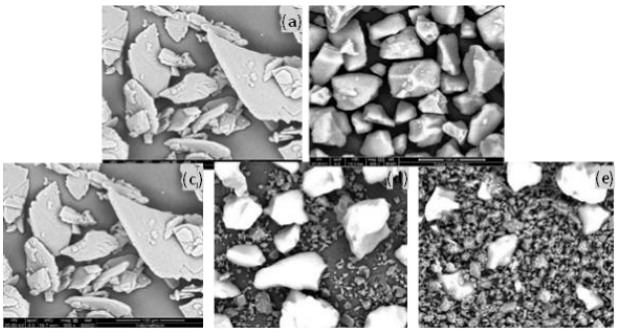

Figure 3. 4. SEM images at x500 of (a) IMC (b) Syloid XDP 3050 (c) MWF of IMC and XDP 3050 (1:1), (d) WWF of IMC and XDP 3050 (2:1), (e) MWF of IMC and XDP 3050 (3:1)

However, the crystals of indomethacin on the surface of the syloid silicas were not evident after microwave formulation. For the 2:1 (x500

magnification) microwave formulation, there was a uniform appearance of some drug molecules on the surface of the silicas.

3.2 *In vitro* indomethacin release

Dissolution studies were performed on pure indomethacin and microwave formulations of indomethacin with three Syloid XDP 3050 silica at 1:1, 2:1 and 1:3 drug-silica ratios to investigate the influence of the silica and microwave on the dissolution behaviour of the drug. The *in vitro* release profiles of indomethacin from Syloid XDP 3050 at the aforementioned drug-silica ratios, along with pure indomethacin in phosphate buffer for 45 minutes, are presented in Figure 3.5.

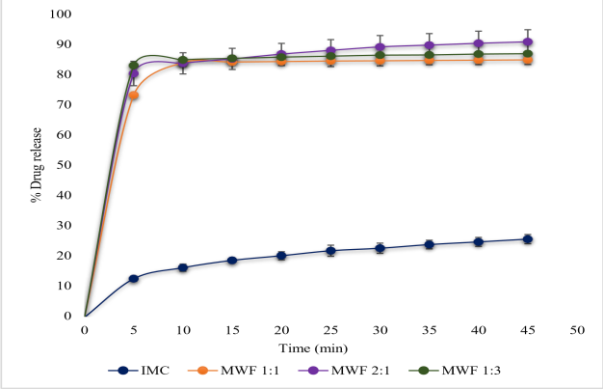

Figure 3. 5. Release profiles for pure indomethacin (IMC) and indomethacin Syloid® XDP 3050-based formulations at 1:1, 2:1 and 1:3. Each data point represents the mean of triplicate results (±SD).

These results highlight that pure indomethacin (that had not undergone the microwave formulation process) exhibited 12.4 % (± 0.8 %) drug release after 5 minutes, yet only increased to 22.4 % (± 1.7 %) after 30 minutes and to a maximum of 25.5 % (± 1.5 %) after 45 minutes. Syloid XDP 3050-based formulations exhibited a significant enhancement in the percentage release, confirming that the formulation of the drug in the presence of syloid using the microwave method contributed to the increase. Formulation of a 1:1 drug-silica ratio achieved a percentage release of 80.3 % (± 0.1 %) after only 5 minutes, while after 30 minutes, the value had increased to 84.6% (± 0.2 %) and 84.8% (± 0.2 %) at 45 minutes. The initial release was attributed to adsorption of the drug into the pores of the XDP 3050 silica [22]. However, a similar drug release profile was observed for the 2:1 drug-silica ratio whereby 83.0 % (± 4.0 %) after 5 minutes was achieved. This was greater than the total seen for the pure drug after 45 minutes.

The reason for this enhanced release has to do with the physicochemical properties of the syloid XDP 3050 [19], and the drug possibly was confined inside the pores and on the surface of the silica. This result fits well with the findings of other studies with mesoporous silica for the release of gemfibrozil [23]. Finally, the 1:3 ratio did show a promising percentage release of 82.8 % (± 10.5 %) after 5 minutes compared with the 2:1, yet after a total of 45 minutes had exceeded further to reach a maximum percentage release of 86.9 % (± 0.4 %). The IMC-XDP 3050 formulation with low silica content (i.e. in 2:1) showed greater drug release while the 1:1 and 1:3 formulations with higher silica content showed an opposite trend. The indomethacin molecules are well dispersed in the silica at higher drug content. In 2:1 ratio, the XDP 3050 partially amorphised the indomethacin by forming an incomplete inclusion complex, this is evidenced by the reduction in the melting peak intensity on DSC thermograms of the ratio (Fig. 3.1). For 1:1 and 1:3 ratios with higher XDP 3050 content, the amount of silica was enough for incorporating IMC, and the interaction of IMC and XDP 3050 was reduced, contributing improved redispersion of XDP 3050 nanoparticles [24].

4. Conclusion

Syloid® XDP 3050 silica significantly enhanced the dissolution of indomethacin when formulated using the microwave-assisted method. Thermal analysis (DSC) of the processed samples showed a marked reduction in the melting endotherm of indomethacin, indicating partial to complete amorphisation. X-ray diffraction (XRD) confirmed this loss of crystallinity, showing the disappearance of sharp diffraction peaks present in the pure drug and the presence of an amorphous halo in the formulations. FTIR spectra revealed no major shifts in characteristic functional group peaks, suggesting that drug–carrier interactions were predominantly physical rather than covalent, supporting the conclusion that the enhancement was due mainly to physical dispersion and nanoconfinement. The dissolution profiles correlated strongly with these solid-state changes: formulations with reduced crystallinity exhibited faster and higher percentage release compared to the crystalline drug. These results are consistent with previous findings for other mesoporous materials [23], where pore confinement and high surface area promoted amorphisation and improved dissolution. In this study, the large pore diameter and moderate surface area of Syloid® XDP 3050 likely facilitated effective drug loading and rapid wetting, maximising dissolution, an effect also observed in other mesoporous microsphere systems [25–26]. Overall, microwave-assisted loading of indomethacin into Syloid® XDP 3050 yielded a higher percentage release than the pure drug, confirming that crystalline-to-amorphous transformation and optimised carrier properties are key to enhancing the dissolution of poorly water-soluble drugs. This approach has potential application beyond indomethacin, offering a promising strategy to improve the bioavailability of a wide range of poorly soluble compounds. Future

research would focus on Comparative studies with other mesoporous silica grades and alternative carriers of varying pore size, volume, and surface chemistry would help clarify structure-performance relationships. Long-term stability studies are also warranted to evaluate whether the amorphous form of indomethacin is maintained during storage under different temperature and humidity conditions.

Conflict of Interest

The authors declare no conflict of interest.

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