https://chemclassjournal.com/
ChemClass Journal Vol. 9 Issue 4 (2025); 115 - 128
e-ISSN:3092-8214 p-ISSN:3092-8206
doi.org/10.33003/chemclass-2025-0904/09

Inclusion of indomethacin in XDP 3050 of Mesoporous silica using wet Methods of formulations

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Abstract

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) characterized by poor water solubility, which negatively affects its bioavailability. In this study, three mesoporous silica excipients (Syloid silica, XDP 3050) were formulated with indomethacin, a model drug with poor aqueous solubility, to enhance the rate and extent of drug dissolution. While other mesoporous silica materials have been investigated in previous studies, the effects of these specific Syloid silica-based excipients in combination with indomethacin remain unexplored. This work demonstrates a significant enhancement in both the extent and rate of drug release for all three Syloid silica formulations at 1:1, 1:2, and 1:3 drug-to-silica ratios over 45 minutes. The dissolution profiles of the three silica types were found to differ, which can be attributed to the physicochemical differences between them. All formulations showed a significant improvement in drug release when compared to the dissolution profile of pure indomethacin. This enhancement is likely due to the large surface area of mesoporous silica, which improves wettability and facilitates drug dissolution. In conclusion, this study confirms that Syloid silica-based excipients can be effectively used to enhance the dissolution and potentially the bioavailability of poorly soluble compounds like indomethacin. Furthermore, the release profiles can be tailored based on the choice of Syloid silica excipient. The latter part of this study also presents the analysis and characterization of indomethacin using Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), Fourier Transform Infrared Spectroscopy (FTIR), and Scanning Electron Microscopy (SEM), with a specific focus on the inclusion of the drug in mesoporous silica.

Keywords: API, DSC IMC.

Introduction

Recently, the pharmaceutical industry has expanded dramatically due to improvement in technological breakthroughs and combinatorial chemistry. All drug contains active pharmaceutical ingredients [API] that are responsible for therapeutic effects. In addition, excipients are added to overcome particular

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issues, for example, to cover an unpleasant taste, to increase the bulk of the drug [diluent] or to reduce cohesion and increase adhesion forces. Some excipients are used to modify drug release and also drug delivery; for example, compounds such as silica polymers and PAMAM dendrimers [1].

The two most important issues in drug manufacturing and discovery are adsorption and solubility, and 1/10 of marketed drugs have solubility problems and over one third of pipeline are sparingly soluble. The solubility of drugs is classified into different types according to the biopharmaceutical classification system [BCS]. Those with high solubility and permeability are termed class 1. Alternatively, class 1 drugs have low solubility and high permeability, while class 1ii drugs have less affinity for permeation through cell membranes. Drugs with low solubility and permeability properties are classified as class 1v [2].

Drugs require a hydrophobic component to be capable of entering through cell membranes. Moreover, they should also have the ability to dissolve inside cells from their hydrophilic properties [1] Different methods have been reported to enhance the solubility of sparingly soluble drugs, for example, a change in the form of the active ingredients to a water soluble salt form, micronasation of drug particles, increasing of the wettability of the drug powder , adding solubilising agent such as surfactant, adding biocompatible drug carriers [liposomes, dendrimers] or formulation the drug inside the pores of silica . All these methods have advantages and disadvantages. There is a significant increase in the solubility of a non–steroidal anti–inflammatory drug [phenylbutazone] using polyamidoamine [PAMAM] dendrimers [3] There are many benefits to using PAMAM dendrimers, firstly, they are more efficient than other carriers [Cyclodextrins or mecelles] due their high density. Secondly, they have a well–defined globular structure, size controlled and thirdly, they have a greater ability to penetrate cell membranes and are safer than protein carriers.

Mesoporous silica has been shown to exhibit great potential to aid in the formulation of pharmaceutical compounds with poor aqueous solubility, as reviewed by [3]. As a drug carrier system, mesoporous silica can accommodate drugs that have been introduced through organic solvent immersion, incipient wetness impregnation or melted in [2]. Specific advantages of using excipients such as mesoporous silicas are their nonporous structures, high surface areas, clinical safety and large pore volumes 9 [5]. Current opinion is that substantial progress has been made in recent years in the characterization and development of mesoporous drug delivery systems although more work is needed regarding dissolution enhancement potential and related physicochemical properties [4]. There are several reasons for this need to continue exploring the possible use of

mesoporous silica including practical considerations such as manufacturability to large-scale quantities (e.g. tonne) and regulation, as well as physicochemical considerations such as the possibility of re-adsorption onto the silica surface [6]. Adsorption of small drug particles on the surface of large excipients has been a successful strategy for low-dose drugs, poor water-soluble drugs, targeted drug release [7]. sustained drug delivery [8] and stability enhancement.

This is mainly a result of improving the dissolution profile by increasing drug surface area or transformation of the drug from a crystalline to amorphous form [9] and its ability to be retained within the silica pores [10]. In many cases, the method of formulation can be critical in defining the properties of the resultant formulation. For example, silica-based drug delivery vehicles have been investigated to avoid hydrolisation of the active compound using supercritical CO_2 [11] a formulation method known for its high drug-loading ability amongst other advantages [12] Several other formulation methods have also been attempted, for example, to create liquid (also known as liquid-solid) formulations and paediatric (solvent free) formulations [13] Previously published studies have confirmed the application of conventional methods for formulation with mesoporous silicas [14]. Furthermore, there is clearly an interest in developing mesoporous silica formulations as evidenced by recent work to predict *in vivo* performance, for example, using *in silico* techniques [15] to overcome multi drug resistance [16] as well as to ameliorate toxic side effects [17].

Methodology

Phosphate buffer

A 8.418 g amount of of potassium dihydrogen phosphate (KH_2PO_4) and 6.644 g of dipotassium hydrogen phosphate (K_2HPO_2) were accurately weighed with an analytical balance (Mettler AT201) and transferred into a 1000 ml volumetric flask, the mixtures were made up to the mark with deionised water, and a pH analyser (Jenway 3510) was used to measure the pH (pH = 7.0) of the solution after shaking for five minutes.

Wavelength determination

A stock solution of 50 μgml^{-1} of indomethacin was prepared in phosphate buffer (pH = 7.0) for lambda max determination, the solution was sonicated (VWR-USC 300T) for 1 hour. Subsequently, a standard solution of 25 μgml^{-1} was prepared in a 25 ml volumetric flask, and a Cary 60 UV/Vis spectrophotometer was used to determine the wavelength of maximum absorption in the range of 200 – 800 nm.

Calibration standard

A Cary 60 UV/Vis spectrophotometer (Agilent technologies) was used to determine the concentration of indomethacin. A stock solution of 50 μgml^{-1} of indomethacin was prepared in buffer, sonicated for 1 hour, then the absorbance

of seven standards solutions (0, 4.0, 8.0, 12.0, 16.0, 20.0, 24.0 μgml^{-1}), each with three replicates, was determined at 292 nm (λmax).

Formulation methods

Syloid silica XDP 3050, 200 mg was placed in a beaker whereupon 40 mL of deionized water was gradually added, followed by 200 mg of indomethacin to achieve a total drug and silica mass of 400 mg. Over a period of 60 min the solution was stirred and heated to a maximum of 90 °C, cooled to room temperature, vacuum filtered and dried overnight at 60 °C, and then sieved to remove agglomerates larger than 250 μm. Buffer of PH 7.0 and temperature of 37°C was used. This process was repeated in triplicate and then with the replacement of XDP 3050 to produce a total of two unique drug-Syloid silica formulations. A series of variable ratios of drug:Syloid drug:Syloid silica formulations was also formulated but based on dissolution profile data, no significant differences in release profiles was observed between the formulations; thus, this paper presents formulations at a 1:1, 1:2 and 1:3 ratios. A final formulation was produced that involved indomethacin undergoing the formulation process (but without the presence of Syloid silica) to determine if it would be the processing that affected dissolution or the presence of each Syloid silica itself. Water was used as a 'carrier' to disperse the drug within the mixture, rather than dissolving the drug with organic solvent, followed by heating to help achieve maximum dispersion within the mixture. However, diffraction peaks were absent in the 1:3 drug to silica ratio products due to the higher silica content, thus confirming that indomethacin had been converted from crystalline to amorphous from upon conventional formulation. Due to the high silica content, a partial crystalline peak of indomethacin was evident in the 2:1 drug to silica ratio-based products. These results were in full agreement with the DSC results reported, confirming an amorphous product was created using conventional formulation with the amorphous silicas.

Characterisation methods

Powder X-ray diffraction (XRD) data was collected on a Bruker D_2-Phaser equipped with a Cu $K\alpha_1$ radiation source at 30 kV and 10 mA current. Particle size distribution of the formulated products was analyzed using a Malvern Mastersizer 2000, using 5–10 mg of powder per sample with one drop of surfactant (IGEPAL CA-630) at a stirring speed of 2000 rpm. Triplicate data was subsequently analyzed using Mastersizer 2000 software (V5.61). Drug loading was verified to be 100% in all 3formulated samples by UV analysis of the filtrates (λ = 282 nm) with no residual drug detected (< 1%), thus confirming all of the drug remained within the formulation (rather than washed away with the filtrate during the formulation process).

Result

Fourier transform infrared spectroscopy (FT-IR)

Figure 1 display the FTIR profiles for IMC, XDP3050, IMC XDP 3050 1:1, 2:1 and 1:3 drug-silica ratio.

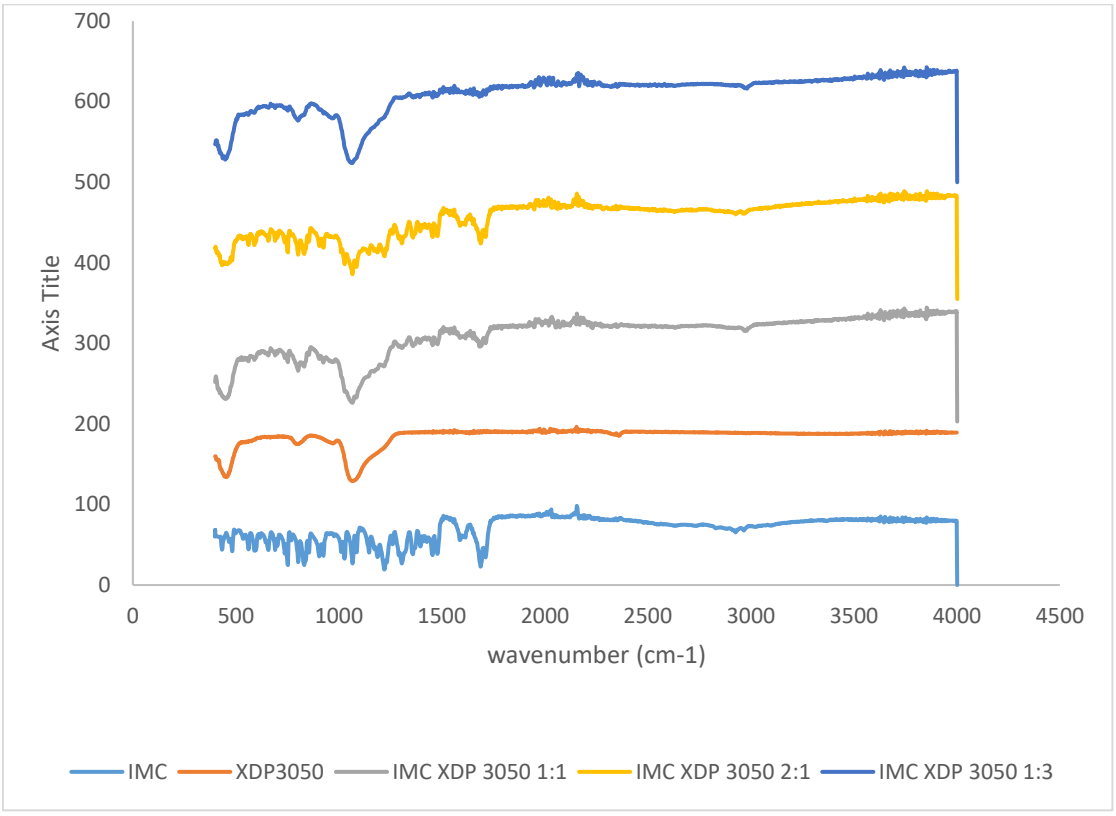


Figure 1: FTIR profiles for IMC, XDP3050, IMC XDP 3050 1:1, 2:1 and 1:3 drug-silica ratio

In this study, characteristics peaks of pure IMC were observed at 3016.7 cm-1 for C-H stretching, 754.4 cm-1 for C-H bending, 2469.8 cm-1 for C-N stretching and 1587.6 cm−1 for C=C stretching vibrations. The FTIR for syloid XDP 3050 is 1014 cm^{-1}, 1259cm^{-1}, 2422cm-1, and 3236cm^{-1}. The absorption bands of IMC were evident in the 2:1 drug to silica ratio. For the three IMC-silica formulated products. The result indicated a significant disappearance of the drug peaks, mainly displaying spectra corresponding to just each type of silica present. Furthermore, the spectra did not display any obvious additional peaks thus indicating there had been no significant changes in the chemical structure or drug-silica interact.

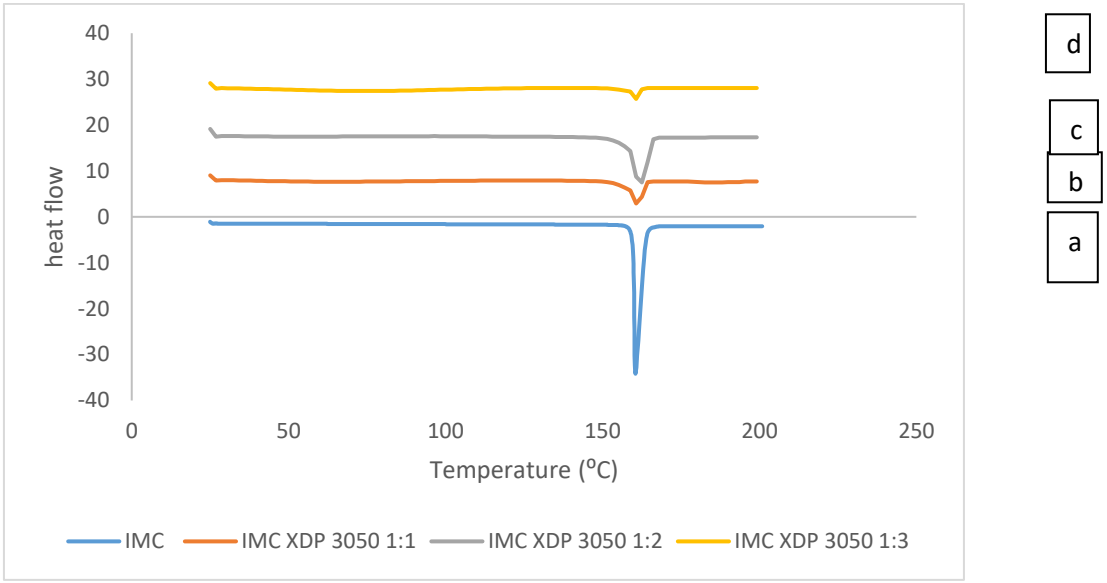


Figure 2: DSC profiles for IMC and XDP 3050 based physical mixture (PM), (a) pure IMC, (b) PM 1:1, (c) PM 2:1 and (d) PM 1:3

Pure IMC displays a sharp peak affirming the crystal nature of the drug. The peak was detected at 161℃. When IMC was formulated with syloid XDP 3050 at 1:1 and 2:1 drug/silica ratios, sign of a melting peak for the drug could be observed at 160.7℃ and 162.5℃. affirming the amorphous nature of XDP 3050 within formulations and this was in good agreement with other XDP measurements (figure 2). In the 1:3 a small peak was detected at 158.8, possibly due to the pore volume of the XDP 3050 which is inadequate for accommodating the extra IMC molecules. The residual drug molecules instead could have resided on the external surface of XDP 3050. DSC confirmed the presence of crystalline IMC in this ratio following the formulation process and this is in good agreement with other XRD measurement (Figure 3)

- X-ray diffraction (XRD) Pattern:

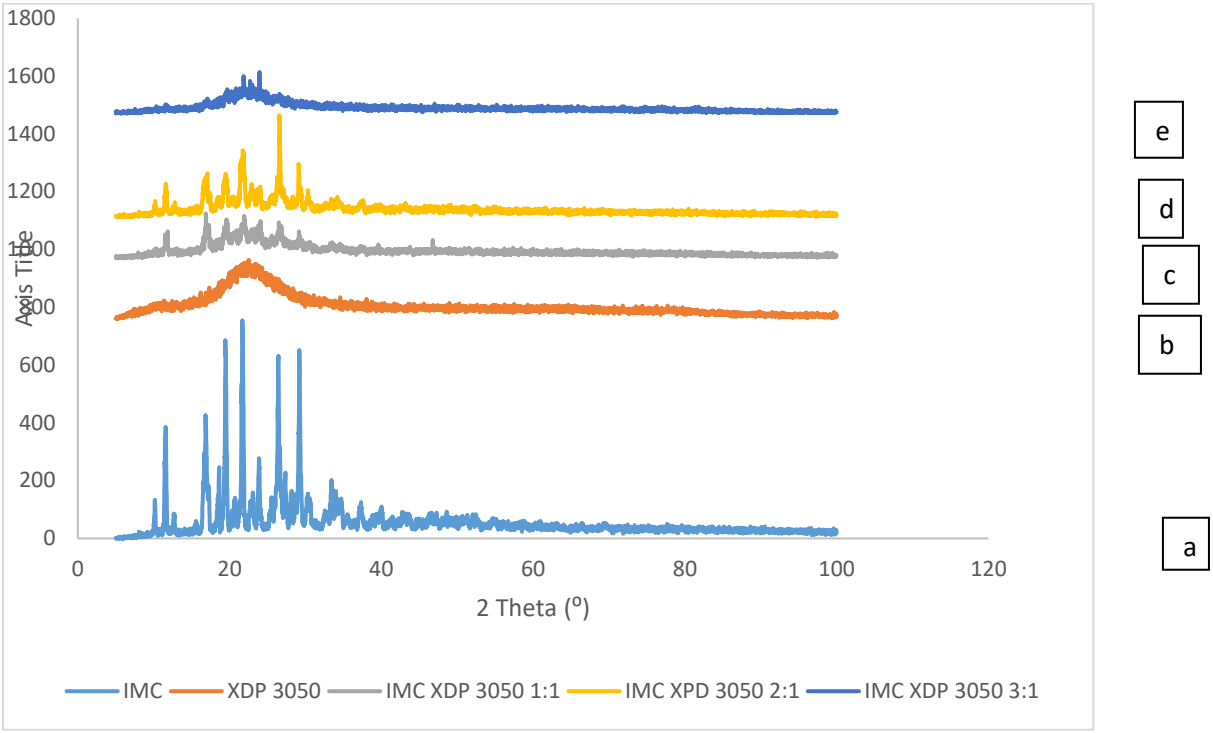


Figure 3: X-ray diffraction (XRD) Pattern

X-ray powder diffraction (XRD) analysis of pure indomethacin, the physical mixtures based formulation with Syloid XDP 3050 and XDP 3051 at ratios 1:1, 2:1 and 3:1 were carried out to confirm this. Figure 3.1 (a) displays the XRD patterns of pure indomethacin with diffraction peaks appearing at 263^0, 350^0, 427^0, 577^0, 652^0, 685^0, 725^0, confirming the crystalline state expected for the drug in comparison with the featureless patterns for the Syloid XDP 3050 (figure 3.) [16, 17]. All the physical mixtures prepared with XDP 3050 displayed peaks, indicating indomethacin was still in a crystalline state. In contrast, the XRD patterns for the 1:1 product formulated (figure 3) indicating small peaks of indomethacin suggesting possibly that the formulation was partially amorphous.

- Scanning electron microscopy (SEM)

  SEM images of pure IMC and physical mixture with syloid XDP 3050 at ratio 1:1, 2:1 and 3:1 (x500 magnifications) were analyzed to investigate changes in morphology.

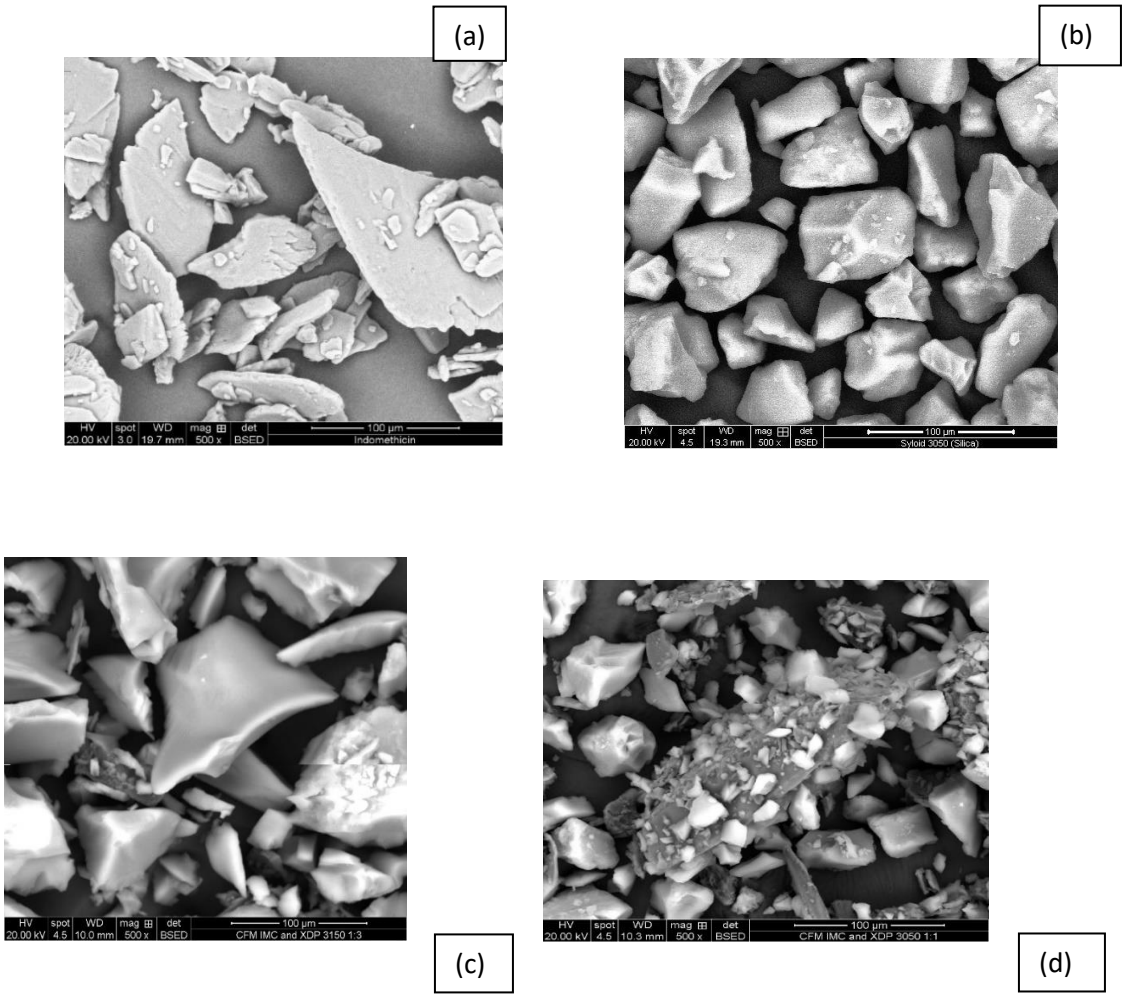


Figure 4. SEM images (x500) of (a) IMC (b) PM of IMC and XDP 3050 (1:1), (c) PM of IMC and XDP 3050 (2:1) and (d) PM of IMC and XDP 3050 (3:1).

Images of IMC and the sylicas are shown in Figure 3.3. IMC particles (Figure 3.3a) have irregular morphology with some of them large and semi rectangular in shape while others are relatively small.

It can be clearly seen in the physical mixture (Figure 4) that drug alone with three syloid silicas do not mix well together as the crystalline state of the drug was maintained. In conventional formulation of the drug with syloid XDP 3050 at 1:1 and 1:3 drug to silica ratios, there is an even

distribution of silica particles but IMC particles are not visible possibly the particles are molecularly dispersed on the surface of the silicas after the formulation. It can be concluded that the IMC is partially amorphous upon formulation with two silicas, as confirmed with DSC and XRD findings. This was attributed to the small pore volume and pore diameter (0.40 $cm^3\ g^{-1}$ and 26 Å) of the silica.

- **Dissolution Studies Profile**

The Table 1 is the dissolution studies of the pure IMC

Table 1: The dissolution of IMC

	Absorbance (A.U)			**Concentration (µgml-1)**			**%Drug Release**				
Time/min	Vessel 1	Vessel 2	Vessel 3	Vessel 1	Vessel 2	Vessel 3	Vessel 1	Vessel 2	Vessel 3	Mean	Stdev
0	0	0	0	-0.1067	-0.1067	-0.1067	-0.4446	-0.4446	-0.4446	-0.4446	0.0000
5	0.114	0.128	0.130	2.7246	3.0571	3.1117	11.3524	12.7378	12.9653	12.3518	0.8730
10	0.172	0.155	0.151	4.1663	3.7270	3.6328	17.3594	15.5294	15.1365	16.0084	1.1864
15	0.188	0.181	0.179	4.5583	4.3722	4.3449	18.9930	18.2175	18.1038	18.4381	0.4839
20	0.207	0.203	0.183	5.0298	4.9206	4.4293	20.9574	20.5025	18.4553	19.9717	1.3328
25	0.216	0.230	0.195	5.2531	5.5980	4.7221	21.8879	23.3251	19.6754	21.6294	1.8385
30	0.223	0.237	0.204	5.4268	5.7742	4.9628	22.6117	24.0591	20.6782	22.4497	1.6963
35	0.234	0.247	0.219	5.6998	6.0124	5.3300	23.7490	25.0517	22.2084	23.6697	1.4233
40	0.243	0.255	0.227	5.9231	6.2308	5.5236	24.6795	25.9615	23.0149	24.5520	1.4775
45	0.256	0.262	0.234	6.2457	6.3945	5.7022	26.0236	26.6439	23.7593	25.4756	1.5184

Table 2 shows the dissolution studies of 2:1

Table 2: Dissolution studies of 2:1

	Absorbance (A.U)				**Active(µg)**		**Concentration (µg/ml)**		**%Drug Release**			
Time(min)	V1	V2	Vol of Vessel (ml)	Sam vol (ml)	V1	V2	V1	V2	V1	V2	Average	Stdev
0	0	0	900	5	14400	14400	0.11	0.11	0.00	0.00	0.00	0.00
5	0.126	0.113	900	5	14400	14400	3.53	3.17	22.04	19.79	20.92	1.60
10	0.218	0.170	900	5	14382.36	14384.17	6.04	4.72	37.77	29.55	33.66	5.81
15	0.272	0.208	900	5	14352.19	14360.56	7.51	5.77	47.07	36.14	41.60	7.73
20	0.312	0.256	900	5	14314.66	14331.73	8.59	7.06	54.01	44.33	49.17	6.84
25	0.331	0.315	900	5	14271.71	14296.43	9.10	8.68	57.39	54.64	56.01	1.95
30	0.356	0.330	900	5	14226.21	14253.03	9.79	9.07	61.91	57.28	59.59	3.50
35	0.404	0.317	900	5	14177.28	14207.68	11.09	8.72	70.42	55.22	62.82	1.40
40	0.421	0.337	900	5	14121.82	14164.09	11.54	9.26	73.55	58.81	66.18	10.42
45	0.423	0.364	900	5	14064.12	14117.81	11.61	10.00	74.27	63.77	69.02	7.43

Table 3 shows the dissolution studies of 3:1

Table 3: Dissolution studies of 3:1

	Absorbance (A.U)				**Active(µg)**		**Concentration (µg/ml)**		**%Drug Release**			
Time(min)	V1	V2	Vol of Vessel (ml)	Sam vol (ml)	V1	V2	V1	V2	V1	V2	Average	Stdev
0	0	0	900	5	5400	5400	0.11	0.11	0.00	0.00	0.00	0.00
5	0.054	0.093	900	5	5400	5400	1.58	2.62	26.36	43.70	35.03	12.27
10	0.135	0.115	900	5	5392.09	5386.89	3.77	3.24	63.00	54.12	58.56	6.28
15	0.162	0.173	900	5	5373.22	5370.69	4.50	4.82	75.33	80.69	78.01	3.79
20	0.182	0.182	900	5	5350.73	5346.62	5.05	5.04	84.97	84.85	84.91	0.08
25	0.170	0.209	900	5	5325.48	5321.41	4.72	5.80	79.82	98.03	88.92	6.30
30	0.163	0.225	900	5	5301.86	5292.43	4.53	6.22	76.90	105.73	91.31	3.50
35	0.183	0.204	900	5	5279.21	5261.35	5.08	5.66	86.54	96.82	91.68	1.40
40	0.167	0.218	900	5	5253.83	5233.04	4.65	6.04	79.74	103.89	91.82	5.70
45	0.187	0.199	900	5	5230.56	5202.84	5.20	5.53	89.45	95.61	91.23	4.36

Table 4 shows the dissolution studies of 1:1

Table 4: Dissolution studies of 1:1

	Absorbance (A.U)				**Active(µg)**		**Concentration (µg/ml)**		**%Drug Release**			
Time(min)	V1	V2	Vol of Vessel (ml)	Sam vol (ml)	V1	V2	V1	V2	V1	V2	Average	Stdev
0	0	0	900	5	10800	10800	0.11	0.11	0.00	0.00	0.00	0.00
5	0.118	0.113	900	5	10800	10800	3.32	3.18	27.63	26.47	27.05	0.82
10	0.165	0.142	900	5	10783.42	10784.12	4.58	3.98	38.26	33.18	44.35	3.59
15	0.197	0.176	900	5	10760.50	10764.24	5.47	4.88	45.77	40.81	57.44	3.51
20	0.217	0.200	900	5	10733.14	10739.84	6.02	5.54	50.45	46.39	61.99	2.87
25	0.220	0.234	900	5	10703.06	10712.16	6.08	6.46	51.09	54.27	65.67	2.24
30	0.234	0.242	900	5	10672.68	10679.86	6.45	6.68	54.42	56.29	68.99	3.50
35	0.247	0.261	900	5	10640.41	10646.47	6.82	7.20	57.67	60.83	70.43	1.40
40	0.281	0.261	900	5	10606.32	10610.49	7.76	7.20	65.82	61.10	71.23	3.34
45	0.273	0.281	900	5	10567.53	10574.47	7.54	7.74	64.18	65.85	71.99	1.18

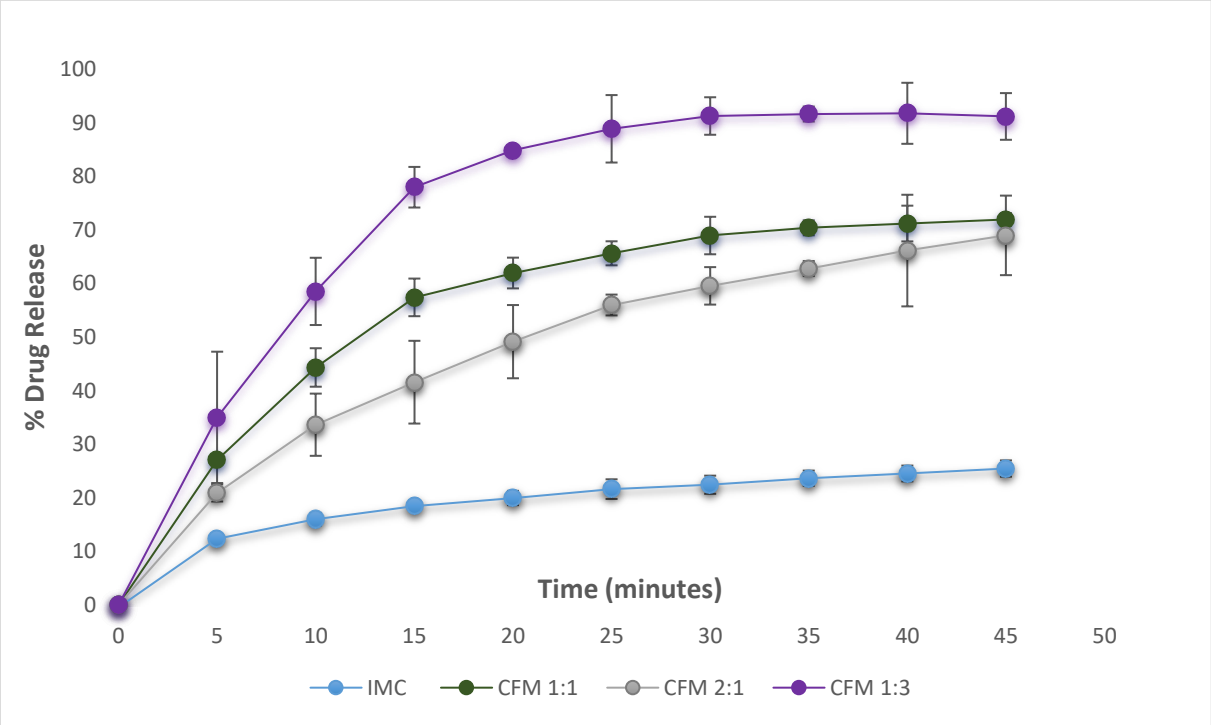


Figure 5: Dissolution profiles using a USP Type II (Paddle method)

Dissolution profiles was determined using a USP Type II (Paddle method) PharmaTest DT70 system, with manual sampling for a period of 45 min. Formulated samples with a total drug content of 22.5 mg was placed in 900 mL of pH 7.0 phosphate buffer, stirred at 75 rpm and maintained at 37.0 ± 0.5 °C, maintaining sink conditions throughout the duration of the experiment. Filtered samples was removed every 5 min, replaced with phosphate buffer, and was analyzed using UV spectroscopy (Cary 60, Agilent) set at a wavelength (λ) of 282 nm with conversion to percentage drug release using a standard calibration plot. Samples was analyzed in triplicate to determine mean drug release perc entages and associated error limits.

Conclusion

In summary, it has been confirmed that it is possible to formulate Syloid silica based formulations to enhance the dissolution of a poorly soluble drug, in this case, indomethacin. Characterization data implies that this enhancement is a result of a change in crystallinity and the ability of the drug to enter pores within the Syloid silica structure. All the Syloid silicas analysed demonstrated a dramatic increase in percentage release with their final percentage values linked to the Syloid silica pore diameter and/or surface area. This finding can be of benefit for not only indomethacin -based equine formulations but potentially a far wider range of compounds that exhibit poor aqueous solubility, which will help alleviate

bioavailability issues. To ensure that long-term stability is not a limiting factor for formulation possibilities, it is the intended subject of future sample analysis, using techniques such as XRD and SEM

Recommendation

Based on the research the following are recommended

- **Further Pharmacokinetic Studies**: To confirm the bioavailability improvements observed in vitro, in vivo studies and pharmacokinetic profiling should be conducted to assess systemic absorption and therapeutic efficacy.
- **Scale-Up Feasibility**: Investigations into the scalability of the wet formulation method should be pursued. This includes optimizing process parameters such as temperature control, drying methods, and mixing time for industrial production.
- **Long-Term Stability Studies**: While the amorphous form improves solubility, it may suffer from poor physical stability over time. Accelerated stability testing should be carried out to assess any potential recrystallization or drug degradation.

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