# Exploring Novel Cocrystals of Milrinone: A Cardioprotective Drug Combined with Nutraceuticals and NSAID

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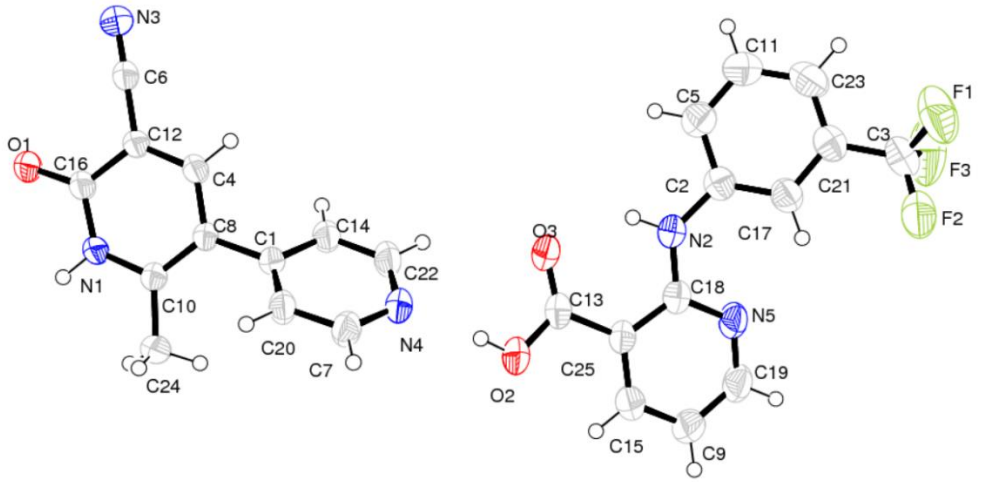
| Parameters | MR.NIF | MR.RES | MR.SES |
|---|---|---|---|
| Formula | $C_{13}$ $H_9$ $F_3$ $N_2$ $O_2$,$C_{12}$ $H_9$ $N_3$ O | $C_{14}$ $H_{12}$ $O_3$,$C_{12}$ $H_9$ $N_3$ O,$H_2$ O | $C_{12}$ $H_9$ $N_3$ O, $C_7$ $H_6$ $O_3$ |
| $M_r$ | 493.44 | 457.47 | 349.34 |
| crystal shape | Block | Block | Block |
| crystal colour | Colourless | Colourless | Colourless |
| crystal system | triclinic | monoclinic | monoclinic |
| space group | $P\bar{1}$ | $P2_1/c$ | $P2_1/c$ |
| $T$, K | 298 | 298 | 293 |
| $\lambda$(Mo-K$_\alpha$)/Å | 0.71073 | 0.71073 | 0.71073 |
| $a$/Å | 10.7282(9) | 12.1866(13) | 8.0120(3) |
| $b$/Å | 10.7734(9) | 14.7266(16) | 16.7621(7) |
| $c$/Å | 11.9845(11) | 26.278(3) | 12.6282(5) |
| $\alpha$/$^0$ | 85.550(2) | 90 | 90 |
| $\beta$/$^0$ | 65.237(2) | 99.145(3) | 91.0102(3) |
| $\gamma$/$^0$ | 64.849(2) | 90 | 90 |
| $V$/Å$^3$ | 1130.01(17) | 4656.0(8) | 1695.68(12) |
| $Z$ | 2 | 8 | 4 |
| $D_c$ / g cm$^{-3}$ | 1.45 | 1.305 | 1.368 |
| $\mu$, mm$^{-1}$ | 0.115 | 0.092 | 0.098 |
| 2θ range [$^0$] | 2.28-24.94 | 2.41 – 24.998 | 2.81-25.242 |
| limiting indices | $12 \le h \le -12$<br>$12 \le k \le -12$<br>$14 \le l \le -14$ | $14 \le h \le -14$<br>$17 \le k \le -17$<br>$31 \le l \le -31$ | $10 \le h \le -10$<br>$22 \le k \le -22$<br>$16 \le l \le -15$ |
| $F$(000) | 508 | 1920 | 728.0 |
| total reflections | 26687 | 68074 | 35954 |
| unique reflections | 3957 | 8213 | 4192 |
| reflection at $I > 2\sigma$ ($I$) | 2954 | 4311 | 2403 |
| No. of parameters | 331 | 632 | 271 |
| $R_1$, $I > 2\sigma$ ($I$) | 0.0502 | 0.0634 | 0.0514 |
| $wR_2$ $I > 2\sigma$ ($I$) | 0.1397 | 0.1847 | 0.1809 |
| GoF on $F^2$ | 1.071 | 0.976 | 1.076 |
| CCDC No. | 2385549 | 2385548 | 2385550 |

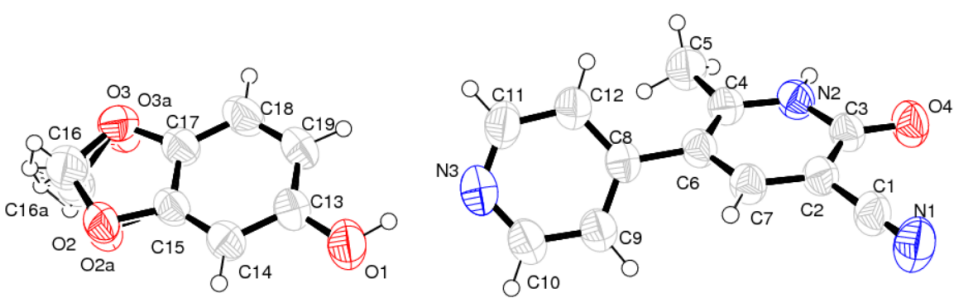
**Table S1.** Crystallographic lattice parameters of MR cocrystals

| | D-H…A | d(D-H)/Å | d(H-A)/Å | d(D-A)/Å | D-H-A/° |
|---|---|---|---|---|---|
| **MR.NIF** | O2-H2….N4 | 0.82 | 1.79 | 2.606(2) | 171.4 |
| | N2-H2A….O3 | 0.86 | 1.96 | 2.665(2) | 138.6 |
| | N1-H1….O1 | 0.893 (17) | 1.868 (17) | 2.760(2) | 177(2) |
| **MR.RES** | N4-H4….O4 | 0.82(3) | 2.06(3) | 2.867(3) | 167(3) |
| | N1-H1….O1 | 0.87(4) | 2.01(4) | 2.866(3) | 169(3) |
| | O2-H2….O9 | 0.819(19) | 1.82(2) | 2.637(3) | 177(5) |
| | O7-H7….N6 | 0.82 | 1.96 | 2.734(3) | 156.5 |
| | O8-H8….N3 | 0.82 | 1.88 | 2.666(3) | 159.3 |
| | O3-H3….O10 | 0.82 | 1.86 | 2.667(3) | 166.6 |
| | O5-H5A….O1 | 0.82 | 1.94 | 2.717(3) | 158.4 |
| | O6-H6….O2 | 0.82 | 1.93 | 2.749(3) | 177.9 |
| | O9-H9A….O8 | 0.85 | 1.94 | 2.783(3) | 174.6 |
| | O9-H9B….O3 | 0.85 | 2.19 | 2.795(3) | 128.0 |
| | O10-H10A….O6 | 0.85 | 2.06 | 2.861(3) | 157.4 |
| | O10-H10B….O4 | 0.85 | 2.00 | 2.811(3) | 160.0 |
| **MR.SES** | O1-H1….N3 | 0.886(18) | 1.83(2) | 2.705(3) | 167(3) |
| | N2-H2….O4 | 0.87(3) | 2.02(3) | 2.864(2) | 164(2) |

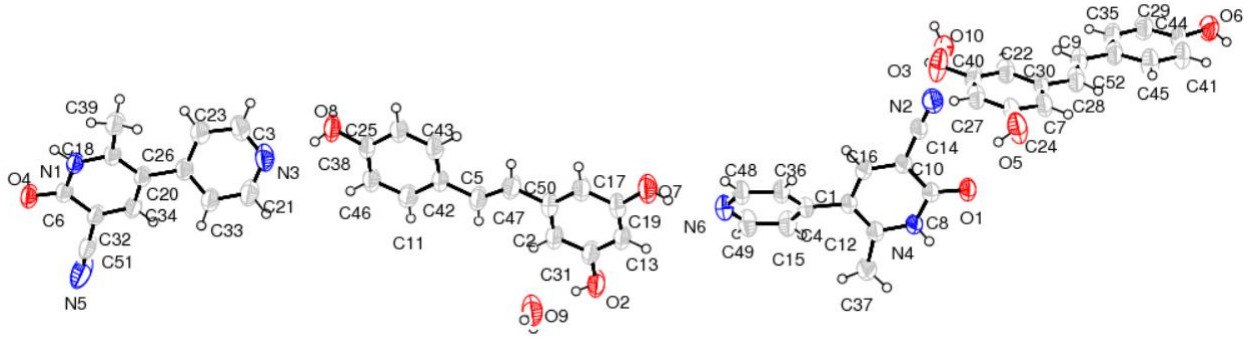
**Table S2:** Hydrogen bond geometry (**Å/°**) of molecular adducts of MR




(a)



(b)




(c)

**Figure S1:** ORTEP view of (a) MR.NIF, (b) MR.SES, (c) MR.RES Co-crystals. Herein, the thermal ellipsoids are drawn with a 50% probability.

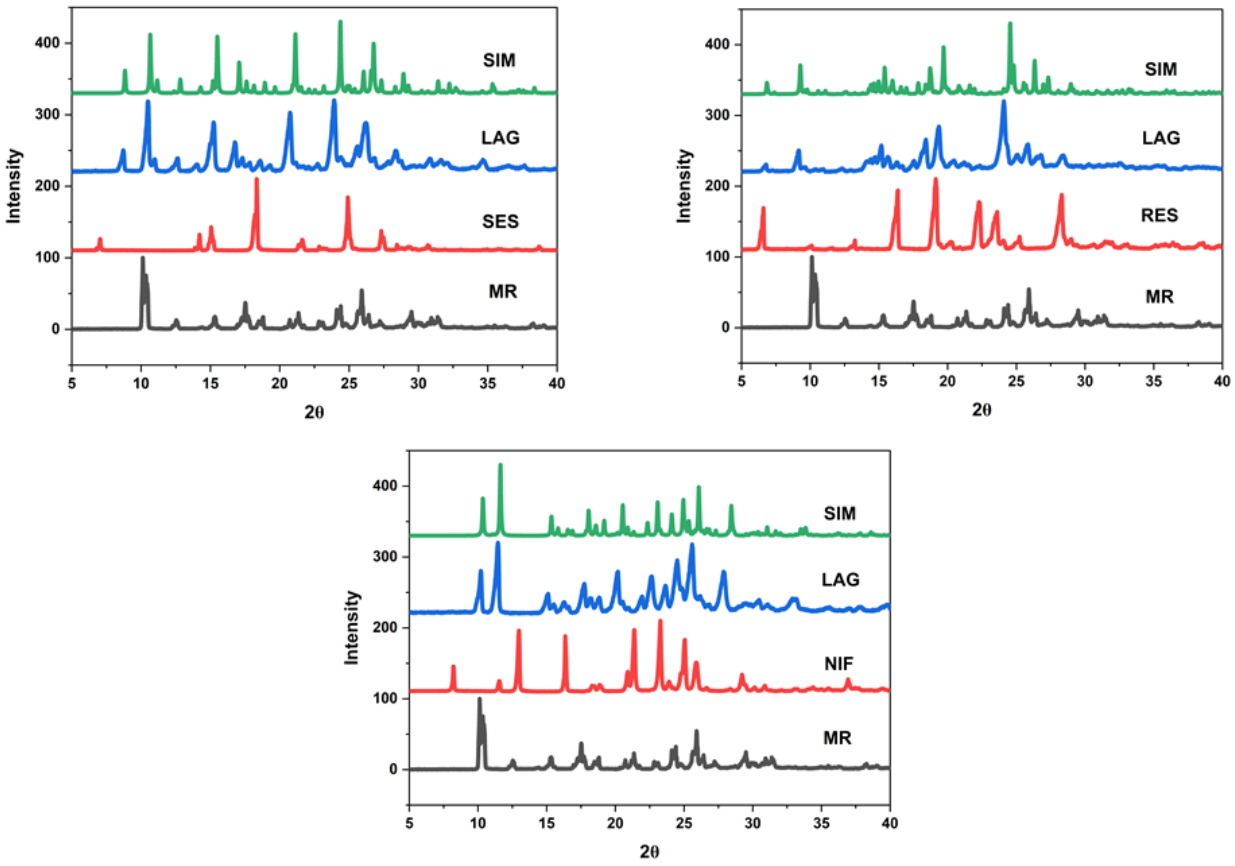



**Figure S2.** PXRD of all synthesized MR.SES, MR.NIF and MR.RES cocrystals confirmed their utmost purity.

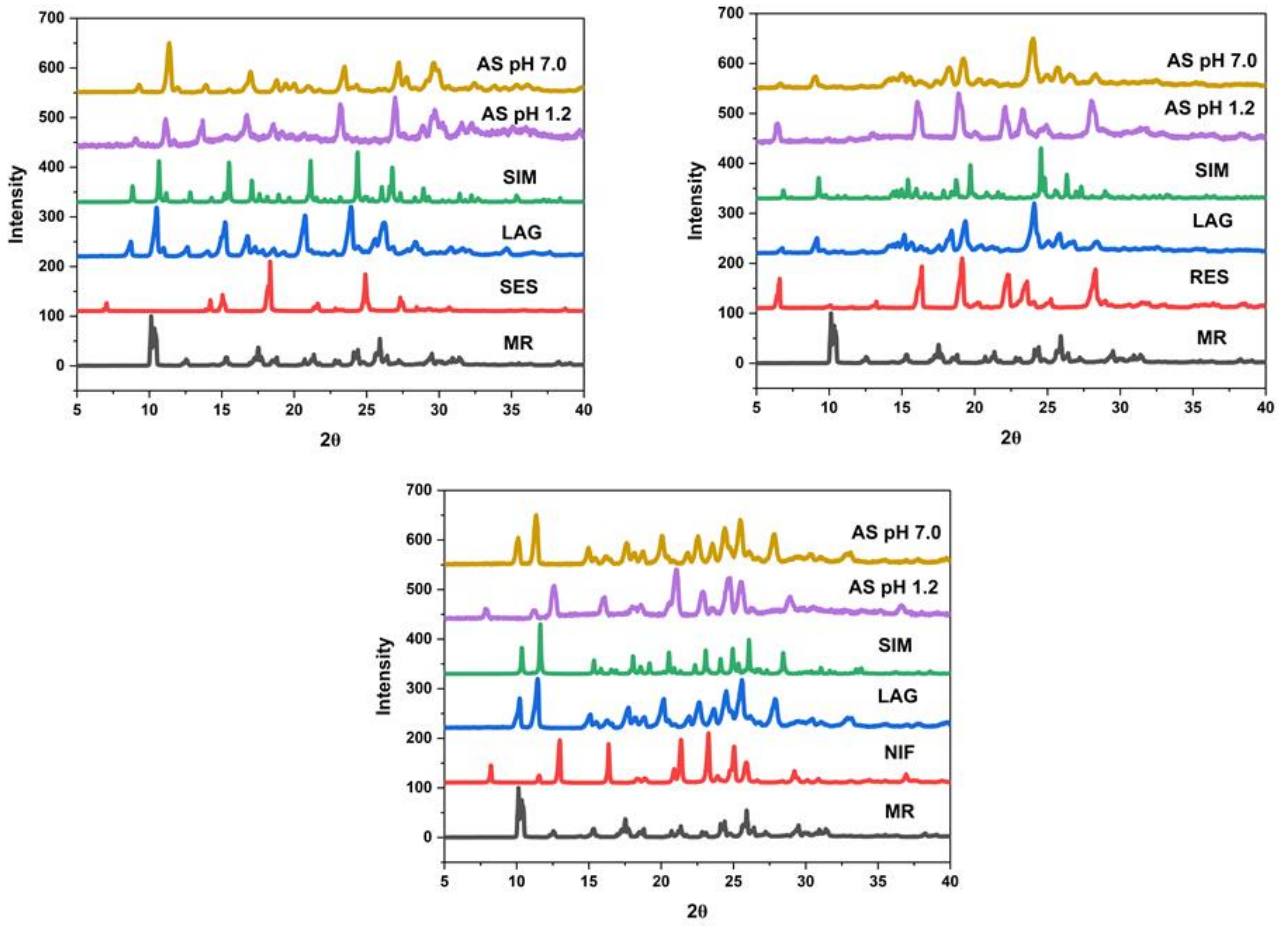
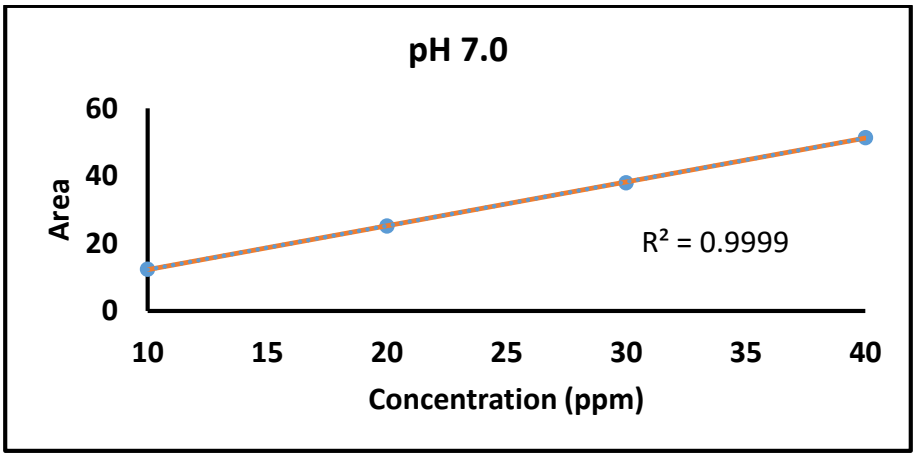
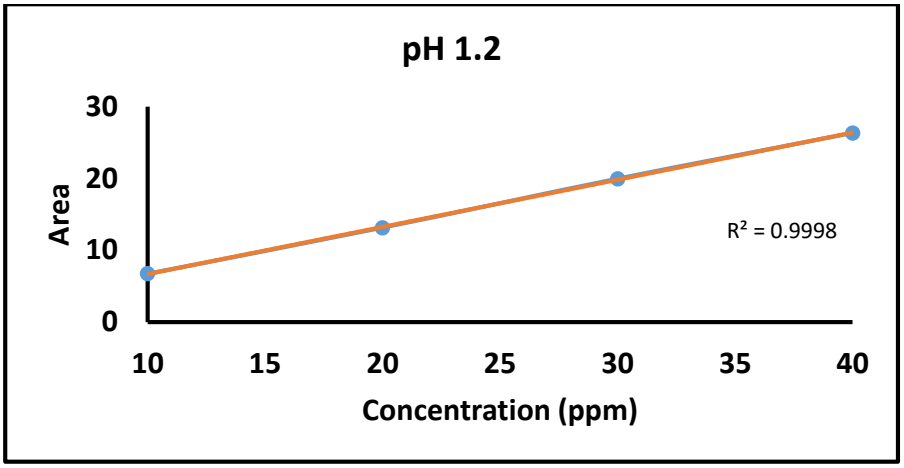



**Figure S3**. PXRD Analysis of all molecular adducts after solubility in both pH 1.2 and 7.0 media




| pH 7.0 | ppm | area |
|---|---|---|
| 1 | 10 | 12.3532 |
| 2 | 20 | 25.1038 |
| 3 | 30 | 37.969 |
| 4 | 40 | 51.2606 |




| pH 1.2 | ppm | area |
|---|---|---|
| 1 | 10 | 6.7188 |
| 2 | 20 | 13.1316 |
| 3 | 30 | 19.9409 |
| 4 | 40 | 26.307 |

**Figure S4:** Linearity graphs for solubility studies of MR and its cocrystals in both pH 1.2 and 7.0 medium.

| Time (minutes) | MR | MR_NIF | MR_RES | MR_SES |
|---|---|---|---|---|
| | Concentration in ppm | | | |
| 15 | 119.7 | 32.9 | 44.4 | 23.2 |
| 30 | 131.3 | 45.9 | 52.2 | 64.1 |
| 45 | 156.7 | 46.3 | 51.2 | 86.1 |
| 60 | 177.4 | 45.5 | 52.7 | 90.3 |
| 90 | 178.5 | 44.8 | 52.5 | 158.6 |
| 120 | 181.7 | 45.5 | 51.9 | 176.4 |
| 150 | 184.7 | 44.6 | 50.5 | 181.9 |
| 180 | 189.8 | 43.1 | 50.1 | 178.9 |
| 240 | 195.2 | 44.9 | 50.0 | 179.8 |
| 300 | 195.7 | 43.7 | 49.5 | 175.2 |

| Compound | Concentration in ppm | | | Standard deviation |
|---|---|---|---|---|
| MR | 1345.3 | 1343.0 | 1343.6 | 0.97 |
| MR_NIF | 377.8 | 378.9 | 375.7 | 1.33 |
| MR_RES | 350.9 | 355.5 | 355.4 | 2.14 |
| MR_SES | 1461.3 | 1466.8 | 1468.7 | 3.14 |

**Table S3.** Dissolution (5h) and solubility (24h) studies of the drug at pH 1.2 medium

| Time (minutes) | MR | MR_NIF | MR_RES | MR_SES |
|---|---|---|---|---|
| | Concentration in ppm | | | |
| 15.0 | 71.8 | 158.9 | 36.9 | 243.3 |
| 30.0 | 148.8 | 273.3 | 61.6 | 416.3 |
| 45.0 | 195.9 | 300.9 | 64.8 | 500.0 |
| 60.0 | 236.5 | 311.7 | 63.4 | 580.6 |
| 90.0 | 287.8 | 321.1 | 64.9 | 624.3 |
| 120.0 | 334.2 | 343.5 | 66.5 | 642.6 |
| 150.0 | 357.0 | 364.1 | 65.5 | 637.6 |
| 180.0 | 369.0 | 372.6 | 64.2 | 631.9 |
| 240.0 | 385.7 | 382.0 | 66.5 | 634.2 |
| 300.0 | 382.5 | 376.6 | 64.2 | 626.7 |

| Compound | Concentration in ppm | | | Standard deviation |
|---|---|---|---|---|
| MR | 531.5 | 533.1 | 540.2 | 3.79 |
| MR_NIF | 371.1 | 372.6 | 372.1 | 0.62 |
| MR_RES | 117.2 | 116.4 | 117.9 | 0.61 |
| MR_SES | 596.6 | 598.8 | 597.3 | 0.92 |

**Table S4.** Dissolution (5h) and solubility studies (24h) of the drug at pH 7.0 medium

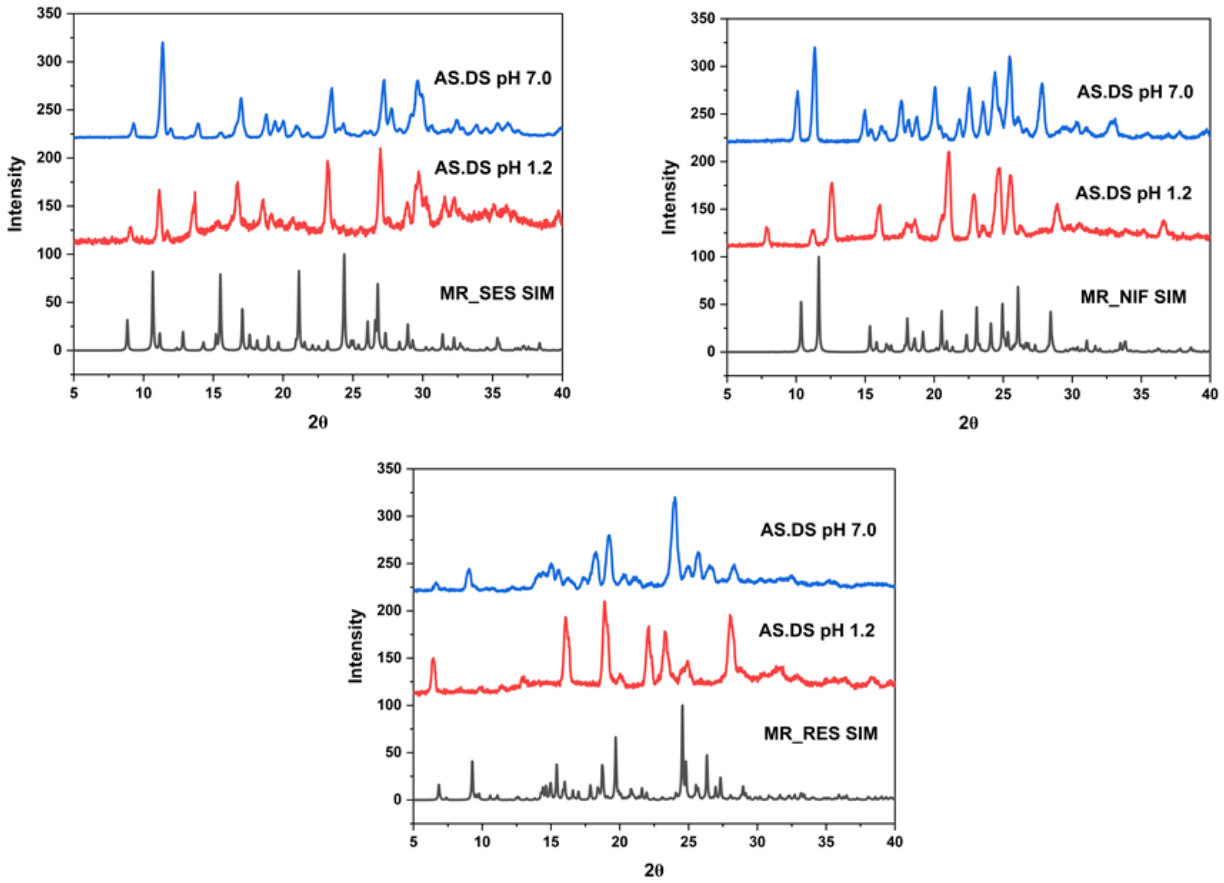



**Figure S5:** PXRD data of all molecular adducts after dissolution in both pH 1.2 and pH 7.0 indicated that MR.SES was stable, whereas MR.NIF and MR.RES partially transformed to either NIF or RES.

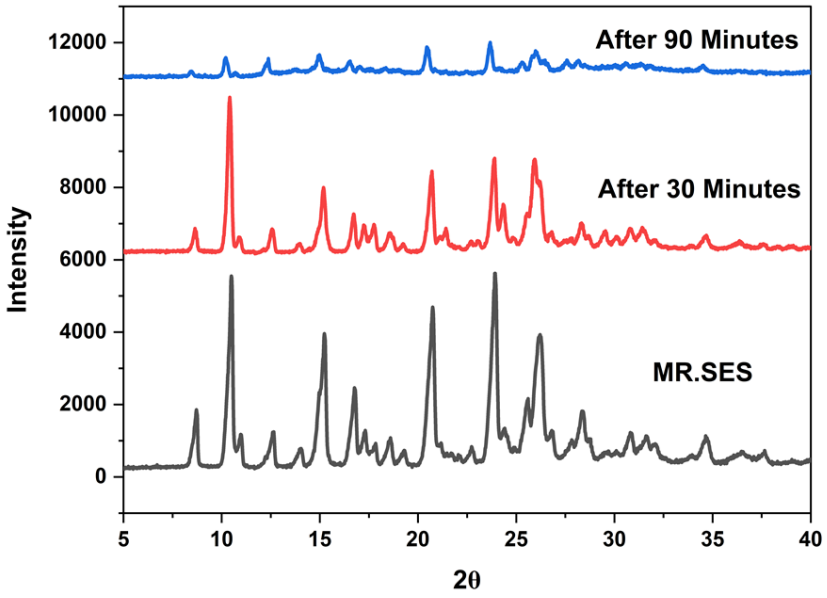



**Figure S6:** Time-dependent PXRD plot of MR.SES during solubility studies at pH 7.0, illustrating structural stability and decrease of particle size over time.

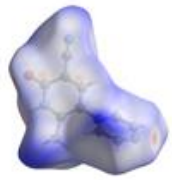
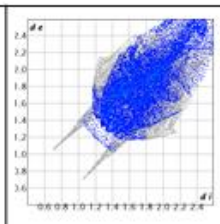
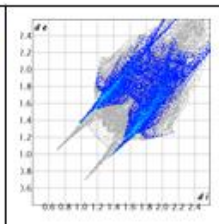
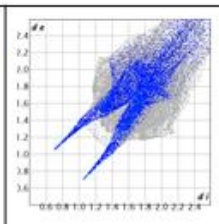
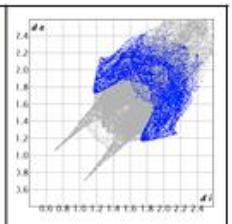
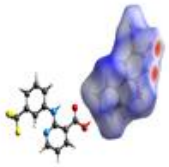
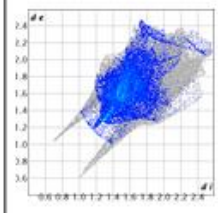
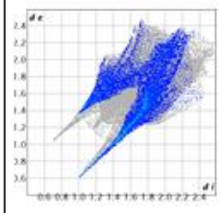
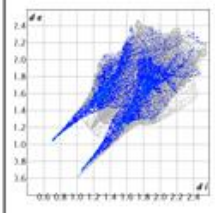
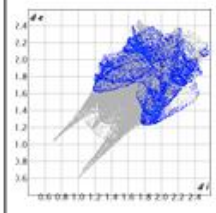
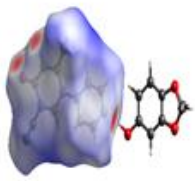
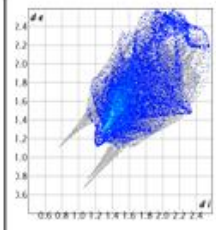
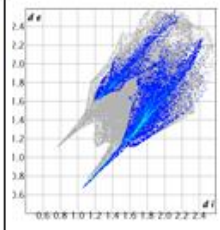
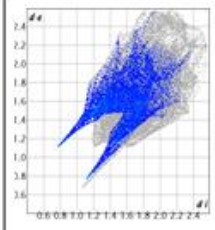
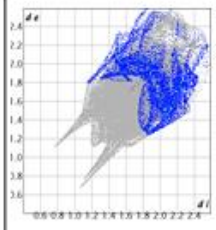
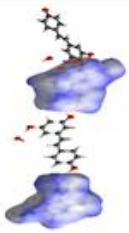
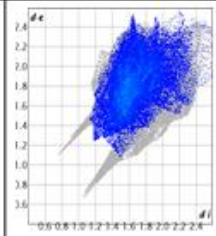
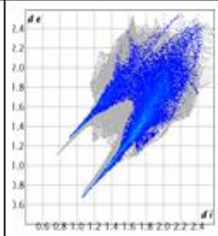
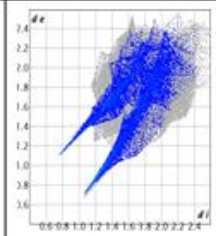
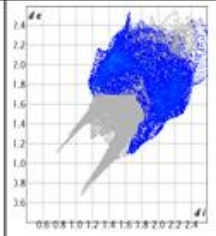
| | | | | |
|---|---|---|---|---|
|  |  |  |  |  |
| MR | H-H-28.1 % | H-N-29.6 % | H-O-14.6 % | H-C-12.9 % |
|  |  |  |  |  |
| MR-NIF | H-H-26.3 % | H-N-21.9 % | H-O-16.8 % | H-C-11.9 % |
|  |  |  |  |  |
| MR-SES | H-H-30 % | H-N-21 % | H-O-20.5 % | H-C-13% |
|  |  |  |  |  |
| MR-RES | H-H-28.5 % | H-N-21.3 % | H-O-15.8 % | H-C-21.2% |

**Table S5:** Hirshfeld Analysis of MR and its cocrystals

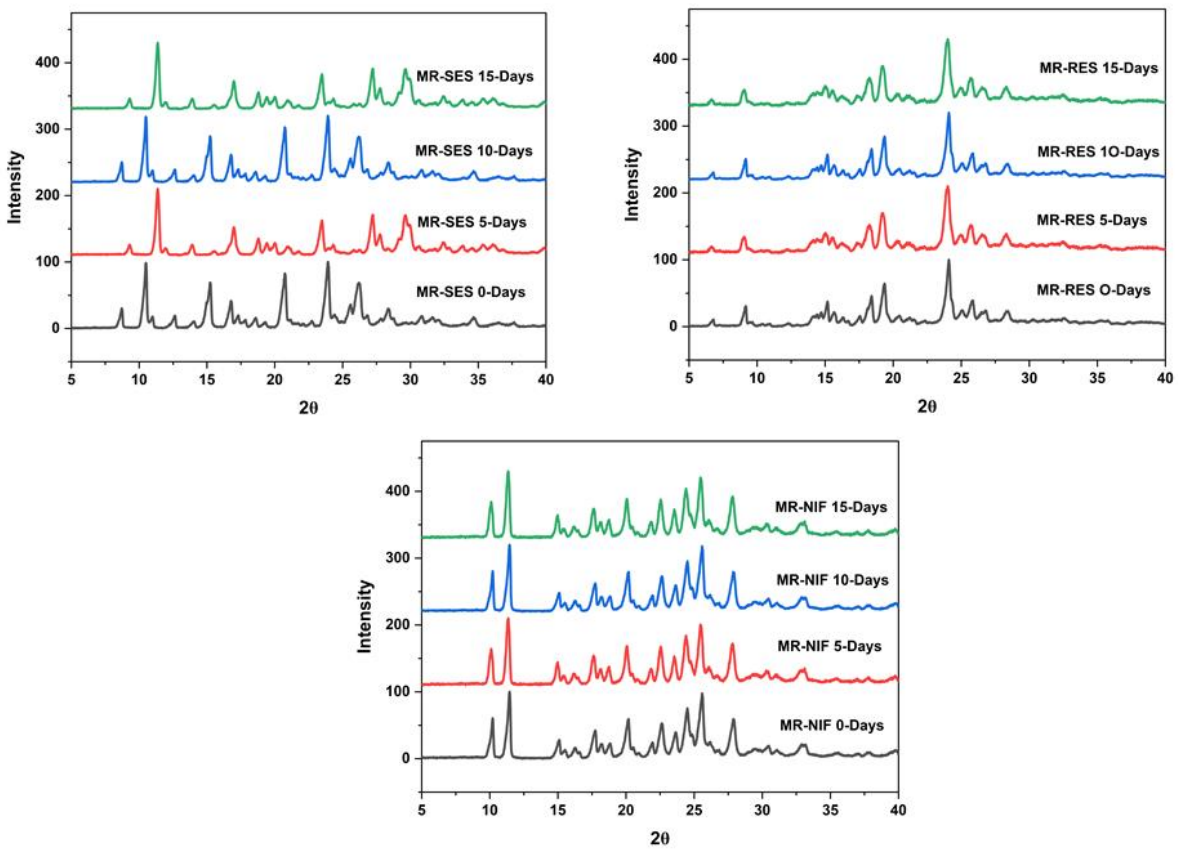



**Figure S7:** Moisture stability studies of all MR cocrystals monitored by PXRD.