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Creativity and Contribution

# PHARMACEUTICAL NEWSLETTER

## Manufacture of Sulindac-Neusilin®
## Amorphous Drug Complex Using Hot Melt Extrusion

# OVERVIEW

## HOT MELT EXTRUSION (HME)

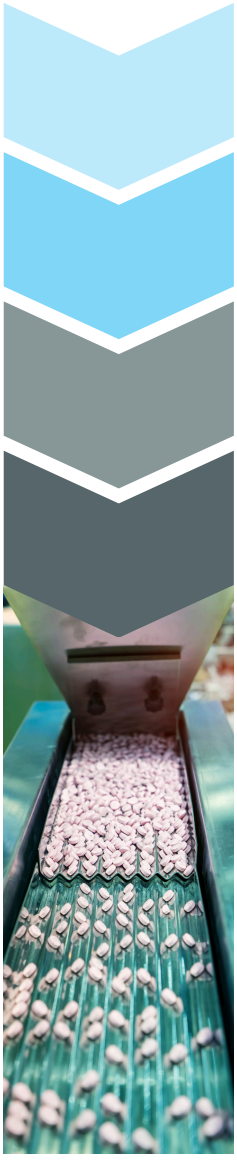
Sulindac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat mild to moderate pain and help relieve symptoms of arthritis.

Hot Melt Extrusion (HME) offers several advantages over traditional pharmaceutical processing techniques such as fewer processing steps, continuous operation, little or no solvents, and commercial scale production of solid dispersions with improved bioavailability. New Chemical Entities (NCEs) with solubility problems are prime candidates for HME.

HME allows dispersion of poorly water-soluble drugs in a given matrix at the molecular level via the formation of a solid solution. The most exciting part of using **Neusilin®** in HME is that solid dispersions can be prepared without any addition of solvents or polymers.

In this newsletter, we report a summary from a recent publication by ***Maclean et al.*** on the ***manufacture of Sulindac-Neusilin® amorphous drug complex via HME.***

## HOT MELT EXTRUSION OF SULINDAC-NEUSILIN® DRUG COMPLEX



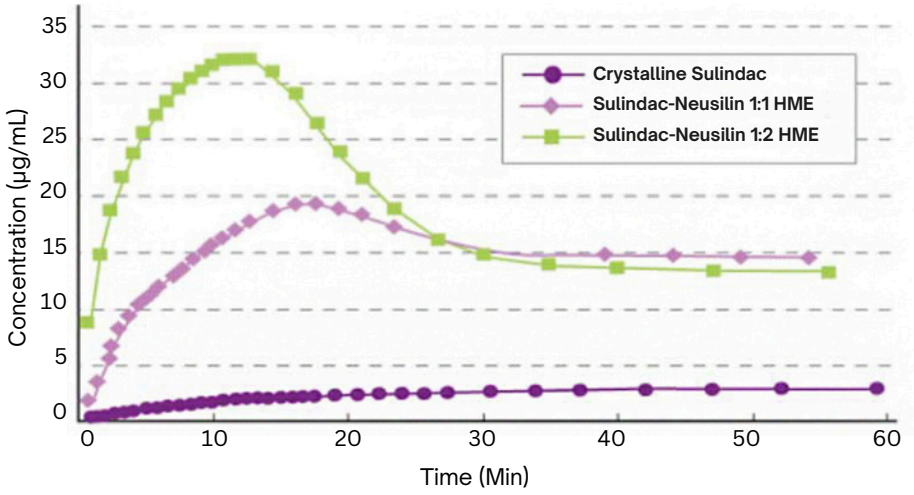
Blends of Sulindac-Neusilin® in 1:1 and 1:2 (w/w ratio) were prepared by mixing the components and charging them to the Brabender single-screw volumetric feeder that fed directly into the extruder hopper at a 5% feed rate.

The material was then extruded using a Prism PharmaLab 16 mm twin-screw extruder (25:1 L/D).

The screw speed was set to 50 rpm for the duration of the extrusion process. Conversion of the crystalline to amorphous complex was observed when HME was conducted at a temperature of 200°C, which is above the melting point of Sulindac.

The sample was recovered as powder from the HME apparatus.
The dissolution profile of the amorphous powder complex is shown in Figure 1.

**Figure 1: Dissolution profiles of amorphous complex and Crystalline Sulindac in 0.1N HCl**

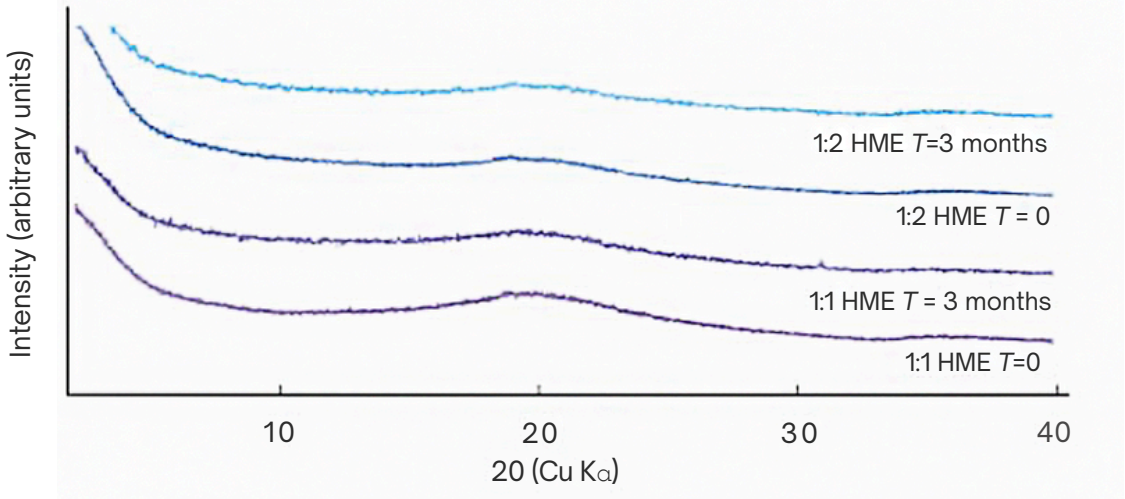


# PHYSICAL / CHEMICAL STABILITY OF SULINDAC-NEUSILIN® HME COMPLEX

The HME samples remained amorphous after 3 months of storage at 40°C/75% RH (Figure 2). The samples were found to remain amorphous for more than one year at ambient conditions. The HPLC analysis during and after the storage period showed no chemical degradation thus confirming the physical and chemical stability of amorphous phase.

The stabilization of amorphous complex is an added advantage over other organic polymer excipients.

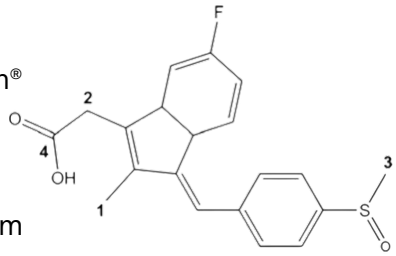
**Figure 2: XRPD data of Sulindac-Neusilin® HME samples as a function of time at 40°C/75% RH.**




**All samples remained amorphous for 3 months at accelerated stress conditions.**

This indicates that the Sulindac-Neusilin® HME samples maintained their physical stability and did not undergo crystallization or degradation during this time period.

# SULINDAC-NEUSILIN® HME TABLETS




Approximately 100 g of 1:1 and 1:2 Sulindac-Neusilin® complexes were produced in this experiment.

Sulindac-Neusilin® complex powder recovered from HME was made into 100 mg, 200 mg and 500 mg tablets through direct compression.

Additional excipients and lubricants were added to match the commercial tablet while keeping the Sulindac weight constant (Table 1).

Tablets were made with crystalline Sulindac plus Neusilin® and HME complex to compare the dissolution profile.

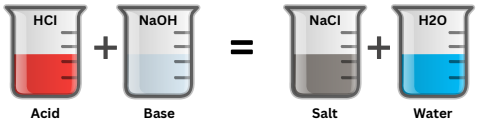
Sulindac- Neusilin® 1:2 HME tablet showed 100% release in 90 minutes as against 9% release of Sulindac-Neusilin® crystalline tablets (Figure 3).

## TABLE 1: COMPOSITIONS OF CRYSTALLINE AND HME AMORPHOUS 1:2 SULINDAC-NEUSILIN® TABLETS

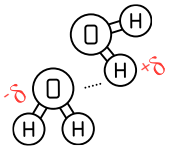
| | 1:1 HME Tablet | | 1:2 Crystalline Tablet | | 1:2 HME Tablet | |
|---|---|---|---|---|---|---|
| **Component** | **Weight (mg)** | **Weight (%)** | **Weight (mg)** | **Weight (%)** | **Weight (mg)** | **Weight (%)** |
| Sulindac | 200 | 40 | 50 | 25 | 50 | 25 |
| Neusilin® | 200 | 40 | 100 | 50 | 100 | 50 |
| Starch 1500 | 47.5 | 9.5 | 20 | 10 | 20 | 10 |
| Avicel PH 102 | 47.5 | 9.5 | 20 | 10 | 20 | 10 |
| Stearic Acid | - | - | 2 | 1 | 2 | 1 |
| HPMC E4 | - | - | 8 | 4 | 8 | 4 |
| Magnesium Stearate | 5.0 | 1 | - | - | - | - |
| **Total Tablet Weight** | **500** | **100** | **200** | **100** | **200** | **100** |

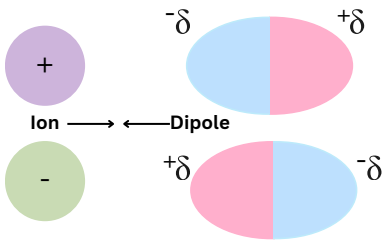
Stabilizing mechanisms of ASD with Neusilin involve:

- Salt formation with acidic drugs like sulindac, indomethacin, ketoprofen, naproxen, ibuprofen and aceclofenac



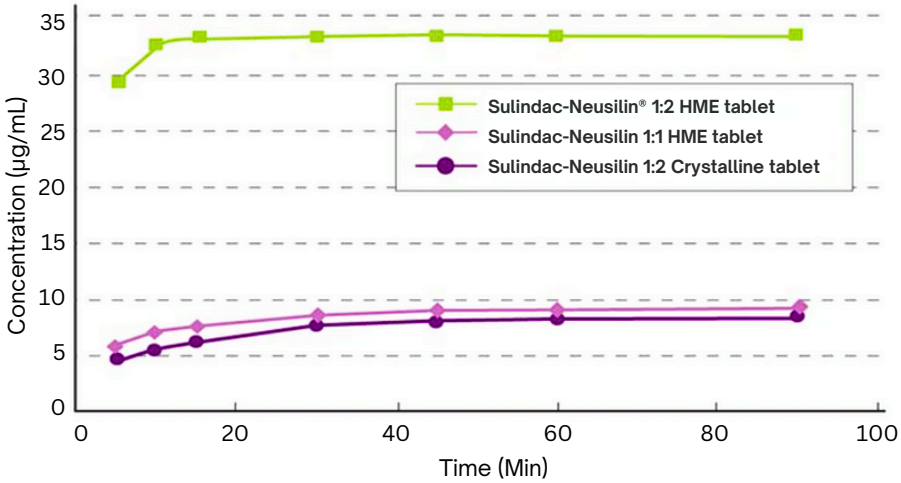

- Hydrogen bonding






- Ion-dipole and dipole-dipole interactions for non-acidic drugs
- Moisture adsorption owing to high specific surface area thus preventing recrystallization of API

## FIGURE 3: DISSOLUTION PROFILES OF HME SULINDAC-NEUSILIN® TABLETS




The tablets containing **Sulindac-Neusilin®** in a 1:2 ratio HME complex achieved complete drug release within 90 minutes. This indicates improved solubility and dissolution properties, potentially enhancing the drug's bioavailability and effectiveness.

## CONCLUSION

- HME was demonstrated as a method capable of large scale manufacturing of stable Sulindac- Neusilin® complex.
- Sulindac-Neusilin® complex can be recovered as powder from HME apparatus.
- No addition of organic polymers was necessary to prepare amorphous form of the drug.
- HME samples remained amorphous after 3 months storage at 40°C/75% RH.
- Both Physical and Chemical stability of the amorphous Sulindac-Neusilin® complex was maintained over 1 year at ambient temperature.
- Tablets made from 1:2 Sulindac-Neusilin® amorphous complex showed 100 % release as against 9% release of crystalline drug.

**Reference**
Jenifer Maclean[1], Cesar Medina[1], Dominick Daurio[1], Fernando Alvarez-Nunez[1], Janan Jona[1], Eric Munson[2], Karthik Nagapudi[1]
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