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*Short communication*

# From granulates to tablets: Influence of compression on indomethacin drug release

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## Introduction

Pain significantly reduces patients' quality of life, and NSAIDs are among the most commonly used drugs for its management. Effective pain therapy requires both rapid onset and sustained drug action. Immediate-release formulations provide fast relief but may require frequent dosing and increase adverse effects, while sustained-release formulations maintain drug levels but have delayed onset and are less suitable for acute pain. Biphasic drug delivery systems can overcome these limitations by combining an initial loading dose with a maintenance dose in a single dosage form, enabling both immediate and prolonged therapeutic effects (Mzoughi et al., 2021).

Indomethacin is a BCS Class II NSAID used in inflammatory conditions such as rheumatoid arthritis, with dissolution-limited absorption and poor compressibility that complicate formulation development (Khomane et al., 2013).

The aim of this study was to develop and evaluate biphasic indomethacin tablets with an immediate (IR) and prolonged release (PR) fraction designed to provide rapid onset and sustained drug release over 6 h.

## Materials and methods

*Materials*

Indomethacin obtained from Xi'an International Healthcare Factory Co., Ltd. (China) was used as the active pharmaceutical ingredient (API). Excipients included silicified microcrystalline cellulose (JRS Pharma, Germany), crosspovidone (Ashland, USA), croscarmellose sodium (JRS Pharma, Germany), sodium lauryl sulfate and povidone K25 (BASF, Germany), hydroxypropyl methylcellulose (Methocel E5, Colorcon, USA), hypromellose K100M (IFF Pharma Solutions, USA), microcrystalline cellulose 102 (IFF Pharma Solutions, USA), colloidal silicon dioxide (Arkema, France) and sodium stearyl fumarate (Syn-Tech Chem & Pharm Co. Ltd, China).

*Preparation and characterization*

Two granulates were prepared by wet granulation: an IR and a PR formulation. The IR granulate contained indomethacin (56.5%), silicified microcrystalline cellulose (39.4%) as filler, crosspovidone (0.6%) and croscarmellose sodium (1.0%) as disintegrants, and a binder solution composed of sodium lauryl sulfate (0.5%) and povidone K25 (2.0%). The PR granulate consisted of

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indomethacin (52.0%), hypromellose K100M (40.0%) as the rate-controlling polymer, Methocel E5 (5.0%) as binder, and silicified microcrystalline cellulose (3.0%) as filler. Both granulates were dried at 50 °C in a tray dryer (MOV212S Panasonic, Japan), sieved through a 0.800 mm sieve, and blended. Extragranular excipients, microcrystalline cellulose 102 (3.1%), crospovidone (1.4%), croscarmellose sodium (2.0%), colloidal silicon dioxide (0.5%) and sodium stearyl fumarate (1.0%), were then added, and the final blend was compressed into tablets (50 mg, 5 mm diameter).

*In vitro* dissolution testing was performed using USP Apparatus II (paddle method) at 50 rpm in 900 mL phosphate buffer (pH 7.2; Ph. Eur. 5.17.1) maintained at 37 °C. Samples were collected at 45 min (IR granulate), 2, 4 and 6 h (PR granulate), and the same time points for tablets. Drug released was quantified spectrophotometrically using a Cary 50 UV–Vis spectrophotometer (Agilent Technologies, USA) equipped with a xenon flash lamp (80 Hz) and 1.5 mm slit width, using a 1 cm quartz cuvette. Absorbance was measured at 265 nm, corresponding to the λmax of indomethacin.

## Results and discussion

The dissolution profile of the IR granulate demonstrated rapid drug release, with 96.42 ± 1.48% of indomethacin released after 45 min, indicating that the IR fraction was capable of providing a prompt drug release. The PR granulate exhibited a slower release compared to IR granulate; however, drug release was still relatively rapid, reaching 81.52 ± 8.21% after 2 h, 89.29 ± 4.70% after 4 h and 91.02 ± 4.51% after 6 h. These results suggest that the matrix system was unable to sufficiently retard drug release and that a large proportion of indomethacin was released within the first 2 h. Following blending of the IR and PR granulates in a 1:1 ratio and subsequent compression into tablets, a markedly different dissolution profile was obtained. The tablets released 19.98 ± 3.37% of indomethacin after 45 min, 31.22 ± 4.83% after 2 h, 44.36 ± 5.01% after 4 h and 54.70 ± 5.35% after 6 h. Compared to the individual granulates, drug release from the tablets was substantially slower throughout the entire dissolution period. The observed reduction in drug release after compression may be attributed to the formation of a more compact structure with reduced porosity and lower effective surface area available for penetration of the dissolution medium. Compression can also enhance particle-particle interactions and decrease the accessibility of drug-containing granules to the dissolution medium, resulting in slower drug release. Furthermore, the presence of both IR and PR granules within a single compact matrix may have altered the hydration and erosion behaviour of the system compared with the individual granulates tested separately.

Although the combination of IR and PR granulates was intended to generate a biphasic release profile, the final tablets exhibited an overall sustained release pattern, with only approximately 20 % of the dose released within the first 45 min and about 55 % released after 6 h. These findings indicate that tablet compression became the dominant factor controlling drug release and largely masked the release characteristics of the individual granulate fractions.

## Conclusion

The results show a clear difference in indomethacin dissolution between granulates and compressed tablets. Although the developed granulates were intended to enable biphasic drug release, tablet compression significantly altered the release behavior and prevented the achievement of the desired biphasic profile. Further formulation optimization is therefore required, particularly through adjustment or selection of alternative polymers to obtain adequate prolonged-release performance.

## References

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