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Short communication

The influence of formulation and hardness on the dissolution rate of ketoprofen in prolonged release tablets

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Introduction

The absorption of a solid dosage form after oral administration depends on three factors: the release of the substance taken, the dissolution of the drug under physiological conditions and the permeability across the gastrointestinal tract. The majority of pharmaceutical products available in the market are in solid dosage forms, such as tablets and capsules, which are practical and widely accepted by patients. Due to the critical nature of the first two of these steps, an in vitro dissolution may be relevant for the prediction of an in vivo performance.

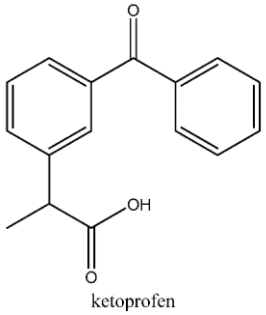
Ketoprofen (Figure 1) serves as an example of a poorly soluble drug. Ketoprofen, also known as 2-(3-benzoylphenyl)propionic acid, is a nonsteroidal anti-inflammatory drug used in the clinical treatment of arthritis and rheumatoid arthritis. Based on the Biopharmaceutical Classification System, ketoprofen belongs to BCS Class II, indicating low solubility and high permeability. In the gastrointestinal fluid, a drug with poor water solubility will experience incomplete absorption (Tsume et al., 2012).

Various approaches have been explored to improve the solubility and dissolution rate of ketoprofen (Browne et al., 2020). The focus of this study is to uncover the concentration of excipients that directly determine the dissolution percentage, as well as the dissolution rate relative to tablet hardness in solid dosage form with prolonged release. To achieve this goal, a total of four experiments were conducted, revealing the following results.

Materials and methods

Materials

Ketoprofen white crystal powder was obtained from BEC Chemicals, Metocel K 4M (Hydroxypropyl methylcellulose) from Colorcon, Natrosol 250 HHX (Hydroxyethyl cellulose) from (Ashland Specialty), Granulac 200 (sharp-edge lactose granules) and Tabletose 80 (agglomerated alpha-lactose monohydrate) from Meggle GmBH. All other excipients were of pharma grade quality.



Fugure 1. Chemical structure of ketoprofen

Methods

Wet granulation: The process of wet granulation was employed to produce granules in a series of four trials. In these experiments, a wet granulation technique was utilized, utilizing a vertical mixer designed for both dry and wet granulation, along with a fluidized bed dryer. The resulting granules were further processed by compression into tablets using a tablet compression machine.

Dissolution Rate Study: The parameter dissolution in four phases is necessary to be performed in glass vessel of the dissolution apparatus with use of sinkers in meaner to avoid adhesion of the tablets on the bottom on the vessel

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of the dissolution apparatus. The dissolution rate was evaluated using a USP/NF <711> Type II dissolution test apparatus with a paddle(Hanson Research SR08; Chatsworth, CA, USA); UV-spectrophotometry; Medium: Phosphate buffer pH 7.2, 1000 mL; Temperature of the medium: 37±0.5ºC; Number of rotations: 100 rpm.

Results and discussion

Each experimental trial differs in two main characteristics: the specific types of excipients used and their percentage composition (Table 1). Specifically, there are four excipients in total, of which only two influence the dissolution rate. Metocel K 4M and Natrosol 250 HHX are the two excipients that affect the dissolution rate. The remaining excipients, such as Granulac 200 and Tabletose 80, are additional ingredients in the composition of extended-release tablets and serve as fillers. The percentage variations of these two types of celluloses reflect the percentage release or dissolution rate of this controlled formulation. In first two trials decreasing the percentage of hydroxyethyl cellulose leads to improved results in terms of dissolution rate, although it does not fully meet the specified criteria. In the experimental trials, third and fourth, where hydroxypropyl methycellulose is used as the controlled-release agent, the results almost align with the specifications. Additionally, during the tableting process, varying the hardness of the tablets has shown to significantly influence the parameter being tested. All four trials involved the tableting of two sets of tablets with different hardness levels. In the first group, the tablets had hardness below 100 N (Table 2), while the second group had a hardness above 100 N (Table 3). The tablets yielded the following results, with significant differences observed in the percentage of release at designated time intervals (three, six, eight, and twelve hours). The tablets with a hardness exceeding 100 N exhibited better and significantly lower values in terms of the percentage of release compared to another group of tablets.

Table 1. Content of excipients in experimental trials

Type of excipients (%)	(T1)	(T2)	(T3)	(T4)
Metocel K 4M	/	/	30.0	25.0
Natrasol 250 HHX	25.0	15.0	/	/
Granulac 200	√	√	/	/
Tabletose 80	/	/	√	√

Table 2. Dissolution rate (<100 N hardness)

Trial	Phase 1 after 3 hours (10 - 25 %)	Phase 2 after 6 hours (20 - 40 %)	Phase 3 after 8 hours (35 - 55 %)	Phase 4 after 12 hours (min 55 %)
T1	15.93	21.05	32.51	43.45
T2	41.34	56.51	70.73	88.80
T3	24.30	38.55	52.18	70.63
T4	28.43	41.20	56.12	79.52

Table 3. Dissolution rate (>100 N hardness)

Trial	Phase 1 after 3 hours (10 - 25 %)	Phase 2 after 6 hours (20 - 40 %)	Phase 3 after 8 hours (35 - 55 %)	Phase 4 after 12 hours (min 55 %)
T1	11.86	16.00	28.50	35.68
T2	29.14	41.33	52.60	65.63
T3	20.28	34.57	43.20	60.15
T4	24.18	38.95	50.21	71.04

Conclusion

Based on the presented work, it can be concluded that there is a noticeable variation in the rate of release among the experiments, indicating a direct influence of the type and concentration of the excipient. The conducted experiments, clearly demonstrate the influence of two polymers and the hardness of the tablets on the percentage of released active substance. On the other hand, drawing conclusions from the conducted trials (experiments three and four), it can be inferred that lower concentration HPMC and higher tablet hardness yield a dissolution pattern that closely resembles the formulation with higher HPMC concentration and lower hardness.

References

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