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DEVELOPMENT AND EVALUATION OF EXTENDED-RELEASE ACEMETACIN CAPSULES USING COMBINED DRY AND WET GRANULATION METHODS

Kübra YILMAZ[*1], Cuneyt TOPRAK[2], Gokay GUN[3], Erdinç BABUÇ[4]

[1]Product Development Senior Specialist, Research and Development Center, World Medicine Pharmaceutical Company, Istanbul, Turkiye.

[2]Scientific Department Manager, Research and Development Center, World Medicine Pharmaceutical Company, Istanbul, Turkiye.

[3]Product Development And Technology Transfer Manager, Research and Development Center, World Medicine Pharmaceutical Company, Istanbul, Turkiye.

[4]R&D Director, Research and Development Center, World Medicine Pharmaceutical Company, Istanbul, Turkiye.

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***Corresponding Author: Kübra YILMAZ**
Product Development Senior Specialist, Research and Development Center, World Medicine Pharmaceutical Company, Istanbul, Turkiye.
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1. ABSTRACT

Acemetacin is a non-steroidal anti-inflammatory drug and the carboxymethyl ester of indometacin. There are many generic drugs of acemetacin on the market but there are only two dosage forms. Those dosage forms are direct effect capsules and extended relaese capsules. The manufacturing process is different in both dosage forms. In this study we tried manufacturing the capsules with different methods. After testing dissolution profiles, we tried to find the best way to manufacture acemetacin capsules.

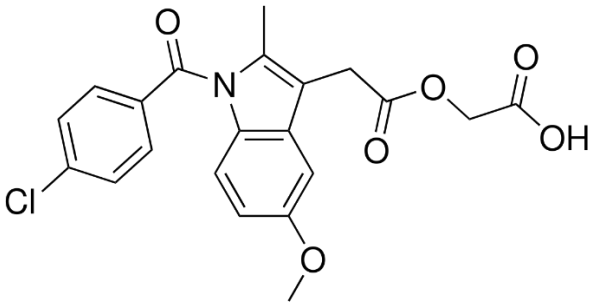
KEYWORDS: Acemetacin, formulation, dissolution, extended relaese, celluloses asetate phytalate.

2. INTRODUCTION

Non-steroidal anti-inflammatory medications are essential for managing pain and stiffness related to inflammatory joint diseases like rheumatoid arthritis, offering symptom relief to countless patients.[1]

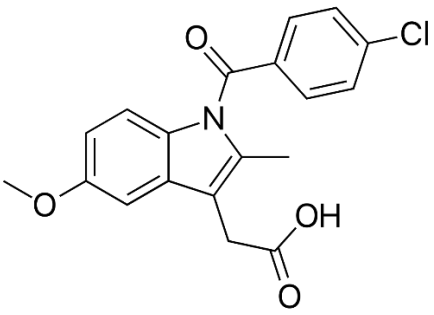
Acemetacin is a carboxylic ester that represents the carboxymethyl variant of indometacin.[2] This non-steroidal anti-inflammatory medication is utilized for conditions such as rheumatoid arthritis, osteoarthritis, lower back pain, and pain

and inflammation following surgery. Its effectiveness comes from both acemetacin and its primary metabolite, indometacin. It functions as a prodrug, acts as an inhibitor of EC 1. 14. 99. 1 (prostaglandin-endoperoxide synthase), serves as a non-steroidal anti-inflammatory agent, and works as a non-narcotic pain reliever. It is classified as an N-acylindole, a monocarboxylic acid, a carboxylic ester, an indol-3-yl carboxylic acid, and belongs to the group of monochlorobenzenes. It is derived from indometacin.[3]



Molecule structure of Acemetacin

Research, both in experimental and clinical settings, has demonstrated that acemetacin is transformed into indomethacin through sterolytic cleavage following oral intake, with significant involvement from the hepatic first-pass effect upon consumption.[4]



Molecule structure of Indometacin

The effect of acemetacin causes a weak reduction of prostaglandin synthesis which generates an anti-inflammatory and analgesic effect. The weak inhibition of prostaglandin reduces significantly the damage caused in the mucous membrane of the gastrointestinal tract. Studies have shown that acemetacin strongly inhibits the release of histamine from mast cells and the generation of hyperthermia. Acemetacin effect also causes changes in systolic and diastolic blood pressure as well as inhibition of platelet aggregation.[5]

Acemetacin is a fine, slightly yellowish, crystalline powder that melts at 150 to 153 °C.[6] The physical form of acemetacin can change by its psd size. If the psd size is lower (micronised) the API is flour like powder, if the psd size is higher the API is in granule form.

In our study we used micronised API for both direct effect form and extended relaese form. After searching we found that the best way to manifacture the capsules of acemetacin is dry granulation method with roller compaction.

3. METHODOLOGY

Wet granulation was selected as the primary manufacturing technique for the development of acemetacin extended-release capsules. This method facilitates the formation of strong interparticulate bonds, enhancing granule mechanical strength and flow properties. Controlled-release polymers are incorporated during granulation to achieve the desired extended-release profile.

3.1. EXTENDED RELAESE CAPSULES

In extended relaese form two batches are made. For the extended relaese capsules, some excipient must be used to get the extended relaese effect. In this formulation, cellulose acetate phytalate is used. For getting the extended relaese effect, after searchings, we found that the best way to manufacturing capsules is using both dry granulation with roller compaction and wet granulation in the manufacturing process.

DRY GRANULATION		**TRIAL 1**	**TRIAL 2**	**TRIAL 3**
1	Acemetacin	30,000 mg	30,000 mg	30,000 mg
2	Lactose monohydrate	-	-	-
3	Talc	-	-	-
4	Silicon dioxide	-	-	-
5	Magnesium stearate	-	-	-
WET GRANULATION				
6	Acemetacin	60,000 mg	60,000 mg	60,000 mg
7	Crospovidone	-	-	-
8	Povidone	-	-	-
9	Cellulose acetate phytalate	16,500 mg	24,150 mg	35,233 mg
10	Dichloramethane	-	-	-
11	Absolute ethanol		-	-
12	Talc	-	-	-
13	Magnesium stearate	-	-	-
	Total	**300,000 mg**	**300,000 mg**	**300,000 mg**

For the %33.3 of the API is used for dry granulation. %66.6 of the API is used for wet granulation. The difference between Trial 01, Trial 02 and Trial 03 is cellulose acetate pyhtalate was %12 of the total batch size. After manufacturing the dissolution profiles are tested and showed in the results section below.

4. RESULTS

4.1. EXTENDED RELAESE CAPSULES

After manufacturing the capsules the dissolition profiles are tested in both batches with different environments. The dissolution environments were, pH:0,1 N HCI+%3 Tween 80 .For the extended relaese capsules dissolution profiles tested and results showed that the profiles were in pH:0,1 N HCI+%3 Tween 80 quite similar. pH:0,1 N HCI+%3 Tween 80 phosphate dissolution profiles showed in Table 3.

Table 3.

TIME (H)	**0**	**0,5**	**1**	**3**	**6**	**9**	**12**	**16**
RANTUDIL RETARD(%)	0,0	20,33	26,19	38,90	47,78	76,94	89,39	91,23
TRIAL 01(%)	0,0	45,32	62,51	79,80	90,13	94,34	96,44	95,63
TRIAL 02 (%)	0,0	19,33	23,51	32,95	45,96	73,57	87,61	90,40
TRIAL 03 (%)	0,0	13,38	16,39	20,85	26,22	28,20	30,71	33,91

5. DISCUSSION

In this study, extended-release acemetacin capsules were successfully developed using a combination of dry granulation with roller compaction and wet granulation techniques. The rationale for combining these manufacturing methods was to optimize both the mechanical strength of granules and the release characteristics of the active pharmaceutical ingredient (API). Cellulose acetate phthalate was selected as the primary release-controlling polymer due to its proven efficiency in modulating drug dissolution, particularly in acidic and neutral pH environments. The dissolution results demonstrated that Trial 02 exhibited the closest release profile to the reference product, Rantudil Retard, across various pH conditions. Specifically, the similarity in release behavior under acidic (pH 0.1 N HCl + 3% Tween 80) conditions suggests that the selected formulation and processing parameters effectively achieved the desired extended-release profile. In contrast, Trial 03, which contained the highest concentration of cellulose acetate phthalate, showed significantly slower drug release, indicating that excessive polymer concentration may hinder drug diffusion from the matrix.

The findings underline the importance of polymer concentration optimization in extended-release formulations. While increased polymer content can prolong drug release, it may also lead to sub-therapeutic plasma concentrations if the release rate becomes excessively slow. Therefore, Trial 02's balanced polymer ratio and granulation approach appear to provide an optimal compromise between extended release and adequate drug availability.

From a manufacturing perspective, the combined granulation strategy improved powder flow, ensured uniform drug distribution, and minimized processing challenges commonly encountered with micronized APIs. Furthermore, this approach may be applicable to other poorly soluble NSAIDs requiring modified release profiles, offering a scalable and reproducible production method for industrial applications. Overall, the study confirms that tailoring excipient ratios and granulation techniques is crucial for achieving target dissolution profiles in extended-release formulations, and that cellulose acetate phthalate remains a robust choice for controlling acemetacin release kinetics.

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7. REFFERENCES

1. P.A.Saul, K.Korlipara, Acemetacin and Indomethacin in the treatment of rheumatoid arthritis a double-lind comperative study in general practice, Current Medical Search and Opinion, 1991; 12(5): 332.
2. P. Sanphui, G.Bolla, U. Das, A. K. Mukherjee, A. Nangia, Acemetacin polymophrs:A rare case of carboxylic acid catamer and dimer systhons, CrystEngComm, 2012; 34.
3. Chemical Entities of Biological Interest, ChEBI, 2017; 31162.
4. A.E. Chavez-Pina, L. Favari, G.Castaneda-Hernandez, Pharmacokinetics of acemetacin and its active metabolite indomethacin in rats during acute hepatic damage and liver regeneration, Annals of Hepatology, 2009; 8(2):141
5. H. Jacobi, H.D. Dell, On the pharmacodynamics of acemetacin, Arzneimittelforschung, 1980; 30(8A): 1348
6. V. Dinnendahl, U.Fricke, Arzneistoff-Profile, 1, Eschborn, Germany: Govi Pharmazeutischer Verlag, 2003.