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Research Article

Formulation And Evaluation Of Ketoprofen Delayed Release Pellets By Using Non-Pareil Seeds

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ABSTRACT

The present study focuses on the formulation and evaluation of delayed-release pellets of ketoprofen using non-pareil seeds as the core material. Ketoprofen, a widely used nonsteroidal anti-inflammatory drug (NSAID), is known for its efficacy in managing pain and inflammation but poses risks of gastrointestinal side effects. To mitigate these adverse effects and improve patient compliance, a delayed-release formulation was developed. The process began with the coating of non-pareil seeds with ketoprofen using a fluidized bed coater. Various polymeric coatings were applied to achieve the desired delayed-release profile, including ethyl cellulose and hydroxypropyl methylcellulose phthalate (HPMCP). The pellets were then subjected to comprehensive evaluation through a series of tests to assess their physical and chemical properties. Key parameters evaluated included: Particle Size and Distribution: Ensuring uniformity and consistency in pellet size. Surface Morphology: Using scanning electron microscopy (SEM) to confirm the integrity and smoothness of the coating. Drug Content: Determining the uniform distribution of ketoprofen within the pellets. In Vitro Release Studies: Conducting dissolution tests to evaluate the release profile of ketoprofen under simulated gastrointestinal conditions. Stability Studies: Assessing the stability of the pellets under various environmental conditions. The results demonstrated that the ketoprofen pellets exhibited a controlled and delayed release profile, reducing the drug release in the gastric environment while ensuring adequate release in the intestinal pH. This delayed-release behaviour is anticipated to reduce gastrointestinal side effects and enhance the therapeutic efficacy of ketoprofen. In conclusion, the formulation of ketoprofen delayed-release pellets using non-pareil seeds proved to be a promising approach for improving the drug's safety and efficacy profile. Further in vivo studies and clinical trials are recommended to validate these findings and explore the potential for commercial application.

Introduction

In the pharmaceutical industry, NPS or Non-Pareil Seeds are used as a core or base for drug formulation, particularly in the production of controlled-release or sustained-release formulations (Ketoprofen gel: severe photosensitisation., 2010) It has many ingredients can be layered onto these sugar cores, and then do drug coating, Seal coating & enteric coating with various ingredients for re lease in SI of drug in the body. This helps provide a consistent and extended release of the drug, improving its efficacy and reducing side effects (Zhang et al., 2018).

DR pellets, also known as enteric-coated pellets or time-release pellets, are small, spherical or granular particles used to deliver medication in a controlled and delayed manner within the gastrointestinal (GI) tract. These pellets are designed to withstand the AM of the stomach and give effect at a specific location in the GI tract, often in the SI or beyond. This controlled release helps improve drug efficacy, reduce side effects, and enhance patient compliance (Shin et al., 2018). Ketoprofen is an analgesic and antipyretic Nonsteroidal anti-

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inflammatory drug (NSAID). It inhibits prostaglandin production IVAIV, maintains lysosomal membranes IVAIV, inhibits leukotriene synthesis in vitro at high doses, and has antibradykinin impact in vivo. Ketoprofen induces analgesia by blocking prostaglandin production both peripherally and centrally. It has also been proposed that ketoprofen suppresses prostaglandin production in the CNS (most likely in the hypothalamus), resulting in its antipyretic action.(Sonita et al., 2023) Ketoprofen is rapidly and nearly fully absorbed from the gastrointestinal system. It is 99% bound to plasma protein, mostly albumin. The elimination half-life of the medication after a single or several oral doses in healthy people has averaged 1.1-4 hours. It is swiftly and thoroughly metabolised in the liver, mostly by conjugation with glucoronic acid. Following a single oral dosage of Ketoprofen, approximately 50-90% of the medication is excreted in urine and around 1-8% in the face within 1-5 days; the majority of urinary excretion happens within 12-24 hours and the majority of faecal excretion occurs within 24-48 hours. Peak concentration of roughly 10mg/L is attained approximately 0.5-0.75 hour after a 100 mg dosage in the event of IM injection. The elimination half-life is around 1.88 hours(Jachowicz et al., 2000).Ketoprofen is used to treat musculoskeletal and joint disorders like ankylosing spondylitis, osteoarthritis, and RA, as well as periarticular disorders like bursitis and tendinitis, mild to moderate pain like dysmenorrhoea or postoperative pain, and other painful and inflammatory conditions like acute gout or soft-tissue disorders, Ketoprofen is used to treat mild to moderate pain, such as postoperative (including dental surgery), postpartum, and orthopaedic (including musculoskeletal strains or sprains) pain, as well as visceral discomfort associated with cancer.(Vishal & Rajashree, 2023) RA is a chronic joint illness. It is also an illness of the system that has the potential to harm internal organs and cause problems in joint. Inflammation of the joint lining tissues promotes joint injury.(Johnson et al., 2023) Inflammation is generally the immune system's response to "assaults" such as infections, wounds, and foreign objects. The inflammation in RA is misdirected and attacks the joints. RA is commonly abbreviated as RA.(Agyilirah et al., 1991). Ketoprofen can produce GI bleeding, decrease platelet aggregation, and increase bleeding duration, it should be administered with caution and the patient should be closely monitored if used with an anticoagulant or thrombolytic medication. Ketoprofen and hydrochlorothiazide used together resulted in lower urine excretion of potassium and chloride when compared to hydrochlorothiazide alone. Ketoprofen and salicylates appear to interact complexly and should not be administered together. The usage of Ketoprofen and probenecid at the same time is likewise not advised. Ketoprofen should be avoided in methotrexate patients.(Jeeraphokhakul et al., 2023)

MATERIALS AND METHODS

DR pellets of ketoprofen was manufactured by FBP method with using drug loading, Seal coating and enteric coating process, Many excipients were used i.e. NPS, HPMC, Polysorbate 80, PEG 6000, SSG, Talc, Acrycoat L30D, Diethyl phthalate, Sodium hydroxide, Titanium dioxide with solvent IPA and PW. (Narala et al., 2023) The enteric coating polymer or pH sensitive polymer played main role in formulation. These types of polymer are meant to release the drug in intestine. If enteric coating process on pellets will not uniform then it could be break in HCl and give release in stomach. (Ramadon et al., 2023)

3.2 Pre-formulation Studies

Pre-formulation investigations are required before the creation of any formulation to detect any changes in drug properties and the eligibility of a drug candidate for formulation development. PF testing examines the drug characteristics and when mixed with another excipients. It is the initial step towards reasonable dosage form development (Hu, Ernst, Benner, & Feenstra, 2021).

3.2.1 Drug Characterization

A white or almost White, Crystalline powder the infrared absorption spectrum of a sample should concordant with spectrum obtained from Ketoprofen working standard the principle peak in the chromatogram obtained with the test solution in similar in retention time and size to the principle peak in the chromatogram obtained with reference solution The solution should be clear and not more intenely coloured . Specific optical Rotation -93º to -96º) Impurity (A, B, C E, F) Not more than 0.2%b) Impurity (G, H, I, J, K & L) Not more than 0.10% c) Total Impurity Not more than 0.4 % (a)Description, identification, Appearance of solution, optical rotation, melting ranges of drug, related substance, heavy metal, water, assay and sulphated ash all the parameters for drug characterization is to be determine by many type of instrument and method.

3.2.2 Drug Solubility

Solubility is the spontaneous interaction of two or more compounds that results in a homogenous dispersion.(Bahr et al., 2023) The solubility of Ketoprofen in several aqueous and non-aqueous solvents was investigated. At room temperature, 10 mg of drug was dissolved in 10 ml of each solvent in screw-capped test tubes.(Marei et al., 2023)

3.2.3 Particle size analysis

Particle size analysis of an active pharmaceutical ingredient (API) is a critical aspect of pharmaceutical development and manufacturing. Apparatus used for particle size analysis is sieve shaker. (Sharma & Saroha, 2023)

3.2.4 Bulk Density Determination

Weighed quantity of pellets (W) was taken in a graduated measuring cylinder and volume (V_o) was measured. (Observation of bulk density shown in Table No. 4.T.4) Bulk Density calculated as:(Vishal & Rajashree, 2023)
Bulk Density = Weight of powder/ Volume of powder (W/V_o g/ml).....eq. 4.2

3.2.5Tapped Density Determination

Weighed quantity of powder was taken in a graduated cylinder and the volume was measured (V_o). The graduated cylinder was fixed in the tapped Densitometer and tapped for 500, 750, and 1250 times until the difference in the volume after consecutive tapping was less than 2%. The final reading was denoted by (V_f), the volume of blend was used to calculate the Tapped density, Hausner's ratio, and Carr's index. (Observation of tapped density shown in Table No. 4.T.4)(Jeeraphokhakul et al., 2023) Taped Density calculated as:
Tapped density = Weight of powder/ Final Volume of powder (W/V g/ml).....eq. 4.3

3.2.6 Hausner's Ratio

Hausner Ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. (Hausner ratio shown in Table Table No. 4.T.4) Hausner ratio calculated as:(Johnson et al., 2023)
Hausner Ratio = Tapped density/ Bulk density (H.R =V_F/V_o).....eq. 4.4
Where, V_F = Final volume, V_o = Initial volume.

3.2.7 Carr's Index

Carr's index is also known as the compressibility index. It is directly related to the relative flow rate, cohesiveness and particle size. It is simple method of predicting powder flow. (Carr's index shown in Table No. 4.T.4)
Carr's Index calculated as:
Carr's Index = (Tapped Density – Bulk Density)/ Tapped Density x 100.....eq.

3.2.8 Drug excipients compatibility Studies

The drug-excipient compatibility study (DECS), which identifies the appropriate excipient to utilize in order to provide a stable formulation/dosage form, is one of the most significant processes in pre-formulation research. As a result, no DECS standards have been suggested. Furthermore, the previously mentioned research and techniques employed by many pharmaceutical companies are time-consuming. As a consequence, a novel vial-in-vial approach for improving existing research strategies and expediting screening of approved excipients during formulation development has been provided. The created approach was compared to previously published traditional procedures that used six different drugs, each with many marketed versions from various manufacturers (Aliberti, et al., 2017).

3.2.9.1 Calibration Curve of Ketoprofen in Phosphate buffer (6.8 pH)

20 mg of ketoprofen was placed in 100 ml of volumetric flask and add phosphate buffer (pH 6.8) and sonicated until completely dissolved. Suitable dilutions of the stock solution were made in decreasing order and analyzed using a UV Visible spectrophotometer at 258 nm, with absorbance values recorded as displayed. (Alshetaili, et al., 2016)

3.2.9.2 Calibration Curve of Ketoprofen in 0.1N Hcl (1.2 pH)

20 mg of ketoprofen was placed in 100 ml of volumetric flask and add 0.1N HCl solution with sonicated until completely dissolved. The solution was suitably diluted with 0.1NHCl solution to get standard concentration of 10, 20, 30, 40, 50, µg/ ml. absorbance was measured at 303 nm UV visible spectrophotometer and absorbance (Andjelić, et al., 2006) values was recorded

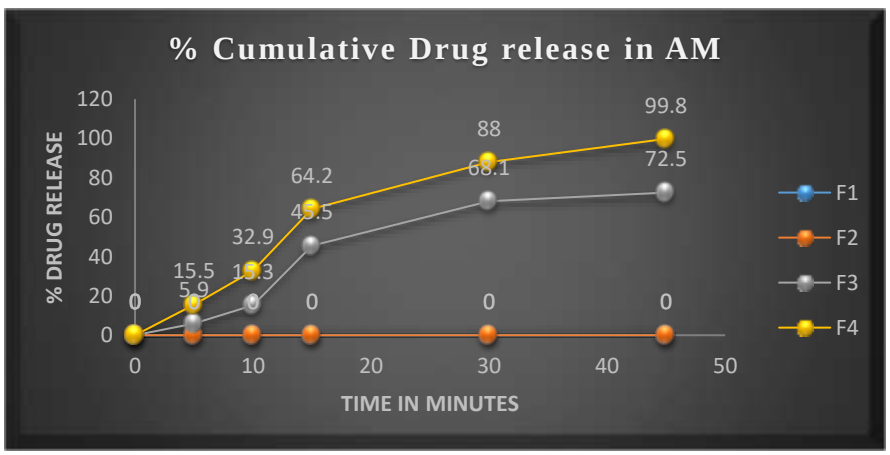

Figure No. 4.F.1 %CDR in AM

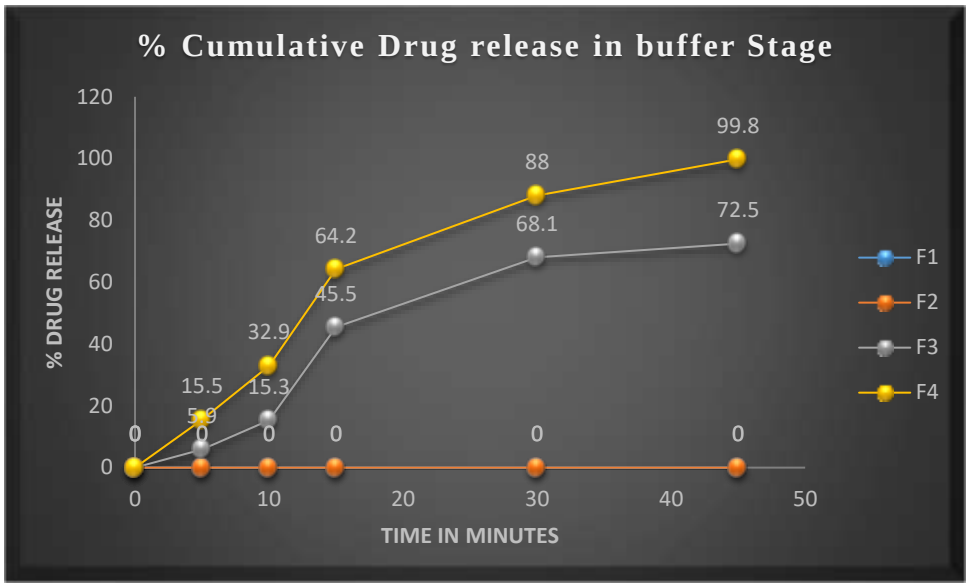

Figure No. 4.F.2 %CDR in Buffer stage

3.3 Formulation development of Ketoprofen DR pellets 26%

In the predetermined research, four type of formulation have been manufactured viz-F1, F2, F3 & F4 with different %weight gain of enteric coating to retard the drug release in HCl to avoid the degradation of drug in stomach. (Cailleteau, 1988), Three trials have been taken for dissolving the drug in Solvents (IPA & water) with adding Polysorbate 80/tween 80 as surfactant to increase the solubility in solvent (IPA & water), Three coating was performed for development of EC pellets of Ketoprofen i.e. Drug coating, Seal coating and Enteric coating. Many ingredients were used in formulation like Superdisintegrants, Surfactant, binding agent, enteric polymer, plasticizer, antitacking agent and solvent. We took different ratio of ingredient in different formulation to make the best and economic formulation. In all formulation, different ratios of polymer were used in preparation of Enteric coating solution (Chawla, Ranjan, Kumar, & Siddiqui, 2017).

Time (In min) In AM	**% CDR**			
	F1	**F2**	**F3**	**F4**
30 minutes	15.3	0	0	0
45 minutes	20.8	0	0	0
60 minutes	61.7	32.8	0	0
90 minutes	85.2	68.4	5.7	0
120 minutes	103.2	83.1	15.3	0
Time (In min) In AM	**% CDR**			
	F1	**F2**	**F3**	**F4**
30 minutes	15.3	0	0	0
45 minutes	20.8	0	0	0
60 minutes	61.7	32.8	0	0
90 minutes	85.2	68.4	5.7	0
120 minutes	103.2	83.1	15.3	0

Result & discussion:

We have taken 10 gm IPA and 5 gm PW in glass beaker and add drug into glass beaker with continuous stirring with glass rod for 5 minutes but it did not dissolve with stirred up to 15 minutes

3.3.1.2 Solubility Study Trial -II

Product Temp	30°C to 50°C
Exhaust Temp	30°C to 45°C
Inlet air flow	20 to 70 cfm
Blower drive speed	25 to 80 %
Peristaltic pump RPM	1 to 10
Atomization	0.2 to 1.5
Process time	To be recorded

A) Drying of EC pellets After seal coating on pellets, drying to be carried out by the following parameters for 30-45 minutes (Wang & Wan, 2015).

Table No.: 5.T.7

Parameters	Set value
Inlet Temp	45°C to 55°C
Product Temp	30°C to 40°C
Exhaust Temp	30°C to 45°C
Inlet air flow	20 to 70 cfm
Blower drive speed	25 to 80 %
Drying time	To be recorded

A) Sifting of dried EC pellets Sift the dried SC pellets through vibro sifter through 14/20# sieve. Collect the oversized pellets in separate polybag. Check the LOD of EC pellets by moisture analyser. Weight the EC pellets to calculate the loss during coating process. (Fossgreen, 1976)

5.2.2 Sachet filling & Sealing:

Set the filling machine with parameters as per specification.Charge the granules in hopper. Rotate the wheel by hands to fill the feed frame with powder. Rotate the machine and disposed off the Sachets filling of initial two to three rounds in sachets disposed container. Ensure that all parameters are within specified limit (Geisslinger, Menzel, Wissel, & Brune, 1995).

5.3 Analytical Method for Finished product

1. Description: Observed visually 20 sachet on white surface for its defects and physical appearance i.e. colour uniformity on pellets, description shall be carried out under indirect day light or under white light (Cailleteau, 1988).

2. Identification (By HPLC): The retention time of the major peak of the sample
Solution corresponds to that of the standard solution (Chawla, Ranjan, Kumar, & Siddiqui, 2017).

3. Average weight: weigh of 20 sachet selected at random and calculate the average weight by weighing balance with following formula (Guy, Kuma, & Nakanishi, 2014).
Average weight= weight of 20 sachet/20

4. Loss on drying:
Take 2 gm pellets and crush in pestle & mortar**.** Set the 80°C temperature in Moisture analyzer and place pellets in tray for LOD. Note the value in percentage (Houghton, Dennis, Rigler, & Parsons, 1984).

5. Pellets size analysis:
Take 10 gm of test sample and sieve through 12# sieve then 18# sieve.
Collect the retained pellets on 18# sieve and weight the retained pellets on 18# and weight the pass pellets by 18# (Hu, Ernst, Benner, & Feenstra, 2021).

6. Assay (By HPLC):
Procedure: The standard solution and sample solution must be protected from light.
Mobile phase: Acetonitrile, glacial acetic acid and water (90:1:110)
Reference Solution: weigh accurately 30 mg of Ketoprofen working standard in 100 ml volumetric flask and add 50 ml mobile phase and stir for 2 hour and make the volume for 100 ml (Zutshi & Mason, 1976).
Test Solution: weigh accurately equivalent to 100 mg of ketoprofen or one sachet in 250 ml volumetric flask, add 150 ml of mobile phase and stir for 2 hours then dilute to mobile phase to volume**,** take 50 ml of solution and centrifuge, Pipet 3 ml of clear supernatant solution into a 100 ml of volumetric flask and dilute with mobile phase to volume (Giovagnoli, et al., 2010).

Table No.: 5.T.8 Chromatographic condition:

Instrument	HPLC with UV detector
Column	4.6 mm X 25 cm; 5-µm packing L1
Flow rate	1.2 ml/min
Wavelength	254 nm
Injection volume	20 µL

7. Residual solvent: For residual solvent test, Gas chromatography (GC) is used to determine with the exception of Class 3 solvents, which can be determined by non-specific analytical techniques such as loss on drying (Jamali & Brocks, 1990).

8. Microbial limit test:

8.1 Total Aerobic microbial count:

Sample preparation: Dissolve or suspend 10g/ml of sample in buffered sodium chloride peptone solution pH 7.0, or phosphate buffer solution pH 7.2 or soya bean casein digest broth or any other suitable medium shown to have no antimicrobial activity adjust the volume to 100 ml with same diluents **(Solution A).** A surface-active agent such as 1g/l of Polysorbate 80 mat added to assist the suspension of poorly wettable substances, if necessary, adjust the pH 6 to 8 (Kantor, 1986).

Procedure: Pipette 1 ml of solution A into each of 2 sterile petridishes of 90 mm in diameter, add to each dish 15-20 ml soya bean casein digest agar that has been previously melted and cooled to 45°C (Luo, Tan, & Luo, 2019). if larger petri dishes are used increase the quantity of agar medium accordingly. cover the petridishes and mix the sample with agar by rotating the plates, allow the contents to solidify at room temperature invert the petridishes and incubate at 30°C to 35°C for 5 days. (Kangasniemi & Kaaja, 1992)

Interpretation of results: After incubation count number of colonies on the plates, take the arithmetic average of the counts and calculate the number of colonies forming units per gram (Mazières, 2005).

8.2 Total yeast & mould count:

Procedure: Pipette 1 ml of solution A into each of 2 sterile petridishes of 90 mm in diameter, add to each dish 15-20 ml Subouraud dextrose agar that has been previously melted and cooled to 45°C (Patra, et al., 2023). if larger petri dishes are used increase the quantity of agar medium accordingly. Cover the petridishes and mix the sample with agar by rotating the plates, allow the contents to solidify at room temperature invert the petridishes and incubate at 20°C to 25°C for 5 days (Kuczyńska, Pawlak, & Nieradko-Iwanicka, 2022).

Interpretation of results: After incubation count number of colonies on the plates, take the arithmetic average of the counts and calculate the number of colony forming units per gram.

CONCLUSION

I have determined that EC pellets of ketoprofen 26% might be the best and most cost-effective formulation in our market for delayed action in SI. Although various commercial versions of Ketoprofen are available on the market. EC pellets of ketoprofen were produced with dibutyl phthalate, and Acrycoat L 30D is now unavailable. Ketoprofen is an analgesic and antipyretic Nonsteroidal anti-inflammatory medication (NSAID). In this investigation, ketoprofen EC pellets were created. The goal of this study was to improve the physical and chemical characteristics of the present formulation by employing appropriate experimental techniques, as well as to improve drug release in the SI. The material and procedure were chosen to assure quality while being cost-effective.

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