FORMULATION AND EVALUATION OF SUSTAINED RELEASE MELOXICAM TABLET FOR TREATMENT OF ARTHRITIS

Miss. Shivani R. Adhav*, Mr. Saurabh L. Nagare, Prof. Mrs. Wakade A. A, Dr. Megha T. Salve

Department of Bachelor in Pharmacy

Shivajirao Pawar College of Pharmacy, Pachegaon, Ahmednagar-413725

Email ID- shivaniadhav02@gmail.com

*Corresponding Author- Miss. Shivani R. Adhav

ABSTRACT:

Meloxicam, a widely used non-steroidal anti-inflammatory drug (NSAID) for arthritis treatment, suffers from a short half-life necessitating frequent dosing and potentially hindering patient compliance. It has greater in vitro and in vivo inhibitory action against the inducible isoform of cyclo-oxygenase (COX-2), which is implicated in the inflammatory response, than against the constitutive form of this enzyme (COX-1), inhibition of which is associated with gastric, renal and other adverse effects. It has anti-inflammatory effects similar to or better than those of other NSAIDs in animal models, and a greater therapeutic ratio (ulcerogenic potential: efficacy in adjuvant arthritis). Sustained release medication is the best choice to overcome these limitations of meloxicam drug. This study aimed to develop and evaluate sustained release meloxicam tablets to improve therapeutic efficacy and reduce dosing frequency for arthritis management.

KEYWORDS: Meloxicam, Conventional formulation, Arthritis, Sustained release tablet.

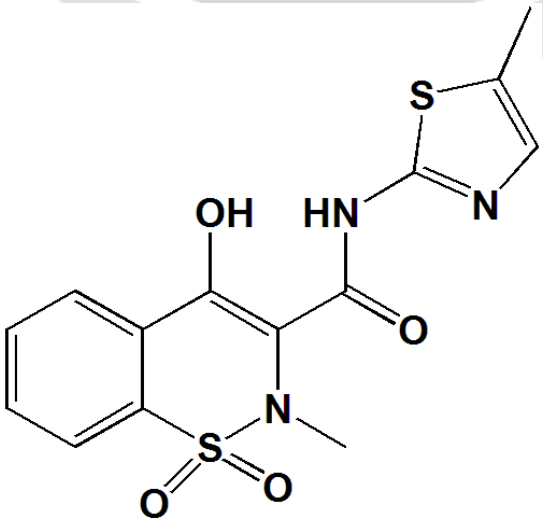
1. INTRODUCTION-

Meloxicam is a new nonsteroidal anti-inflammatory drug (NSAID). In contrast with other NSAIDs currently available, it appears to have greater inhibitory activity against the inducible isoform of cyclo-oxygenase (COX-2), which is im-plicated in the inflammatory response, than

against the constitutive isoform (COX-I), inhibition of which is associated with gastrointestinal and renal adverse events and inhibition of platelet aggregation. Meloxicam has been approved in France and several other countries for the treatment of rheumatoid arthritis and osteoarthritis, is in pre-registration in additional countries worldwide and is in clinical development in the US and Japan. [1] Meloxicam, sold under the brand name Mobic among others, it issued to treat pain and inflammation in rheumatic diseases and osteoarthritis. It is used by mouth or by injection into a vein. It is recommended that it be used for as short a period as possible and at a low dose. Common side effects include abdominal pain, dizziness, swelling, headache, and a rash. Serious side effects may include heart disease, stroke, kidney problems, and stomach ulcers. Use is not recommended in the third trimester of pregnancy. It is in the oxicam family of chemicals and is closely related to piroxicam. Meloxicam was patented in 1977 and approved for medical use in the United States in 2000. It was developed by Boehringer Ingelheim; however, it is also available as a generic medication. In 2021, it was the 32nd most commonly prescribed medication in the United States, with more than 18 million prescriptions. An intravenous version of meloxicam (Anjeso) was approved for medical use in the United States in February 2020. [2]

Chemistry-

Meloxicam is an enolcarboxymide NSAID related to piroxicam. Its chemical designation is 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzo-thiazine-3-carboxamide 1,1-dioxide and has a chemical structure as shown in Figure 1. Meloxicam has a molecular weight of 351.4. It is available as a tablet in 7.5 and 15 mg strengths in the US. In Europe it is also available as an oral suspension and in an intramuscular injection form. [3]



Mechanism of action-

The mechanism of action of meloxicam is probably identical to all other NSAIDs in that it inhibits prostaglandin synthetase. Meloxicam has shown anti-inflammatory, analgesic and antipyretic activity in animal models. In vitro studies have confirmed that meloxicam preferentially inhibits the inducible COX-2 of cultured guinea-pig peritoneal macrophages and is more effective in inhibiting COX-2 compared to the constitutive enzyme, COX-1 [4]

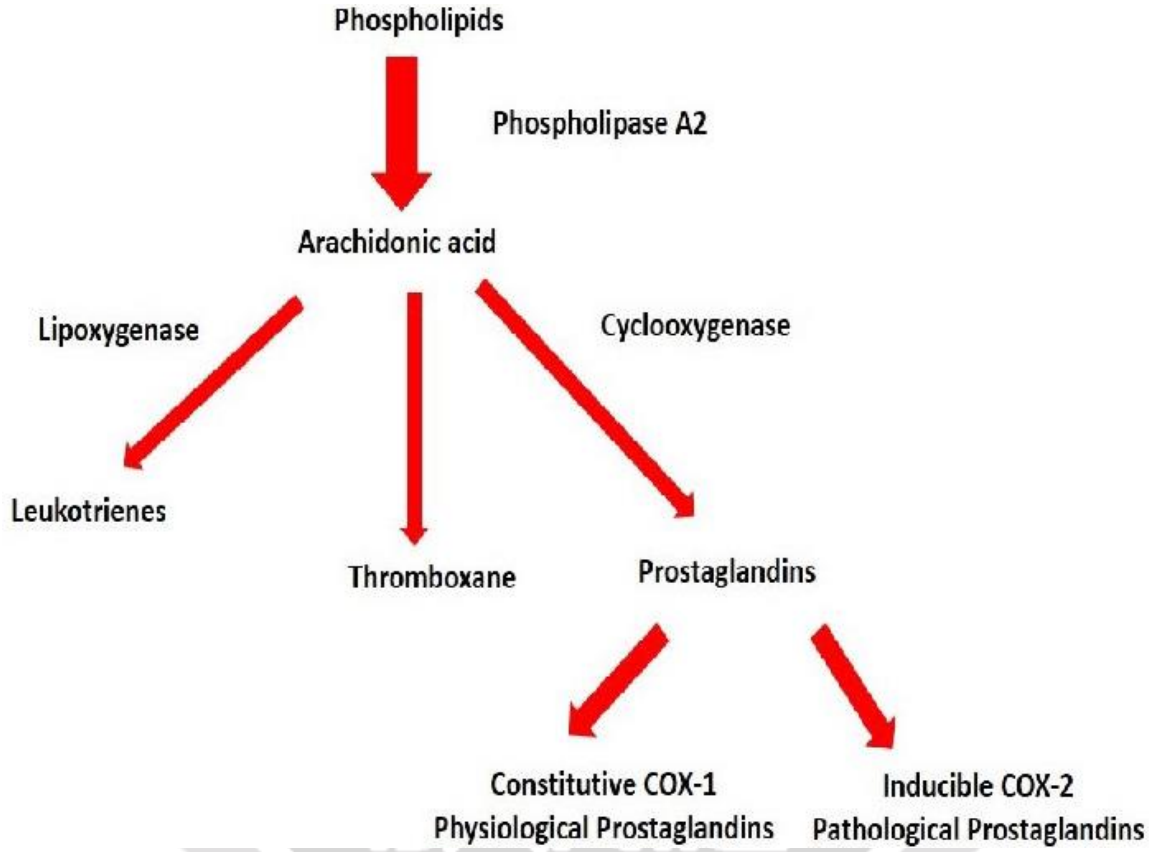


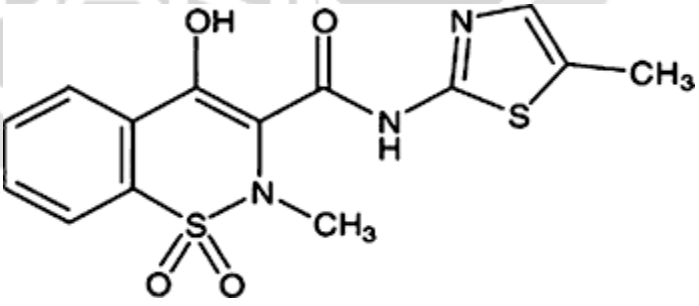
Fig 1. Mechanism of action of meloxicam. [5]

Pharmacokinetics-

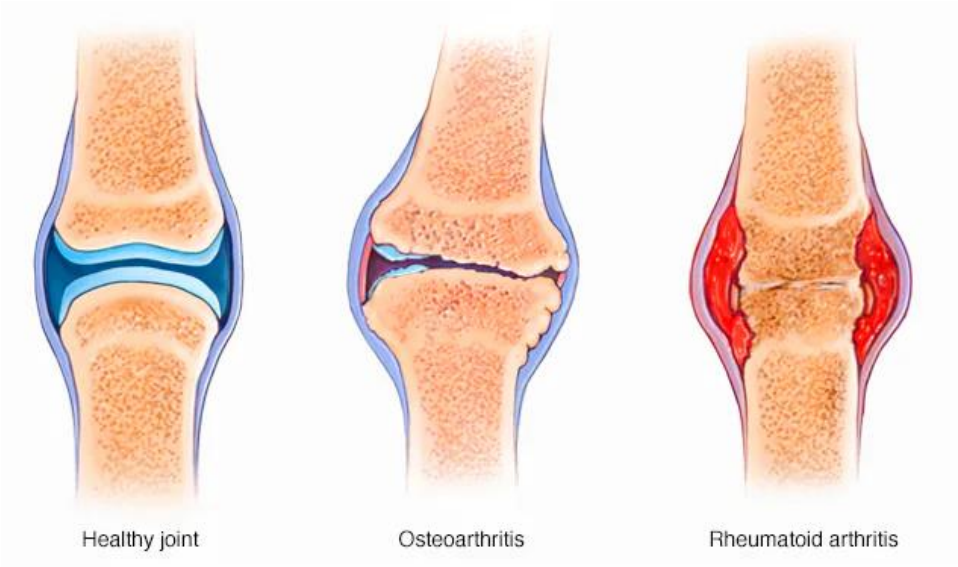
D. Turck and collogues, prepared a review of the clinical pharmacokinetics of meloxicam. They concluded that the pharmacokinetic profile of the drug is characterized by a prolonged and almost complete absorption, and that the drug is more than 99.5% bound to plasma proteins. Peak plasma concentrations occur within 6 h. Meloxicam is metabolized to four biologically inactive main metabolites, including its major metabolite, 50-carbox-ymeloxicam. They are excreted in both urine and feces. The elimination half-life (t½) of meloxicam is approximately 20 h. This is reflected in a total plasma clearance (CL) of 0.42e0.481/h. Steady-state plasma

concentrations are achieved within 3e5 days. The pharmacokinetic parameters of meloxicam are linear over the dose range 7.5e30 mg and bioequivalence has been shown for a number of different formulations. The pharmacokinetic profile of meloxicam in the rat is similar to that in man. No interactions were observed following the concomitant administration of food, cimetidine, antacid, aspirin, b-acetyldigoxin, methotrexate, warfarin or furosemide. Neither hepatic insufficiency nor moderate renal dysfunction have any relevant effects on the pharmacokinetics of meloxicam and dosage adjustments in the elderly are not required. [6,7]

Drug profile [8,9]

Drug name	Meloxicam
Indication	Treatment of arthritis, osteoarthritis, pain, swelling, stiffness, and joint pain
Mechanism of action	It is a NSAID preferentially inhibits the inducible COX-2.
Chemical name	4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)-1,1-dioxo-1λ6,2-benzothiazine-3-carboxamide
Chemical Structure	
Route of administration	Oral administration is effective.

Arthritis- [10]



"Arthritis"

literally means joint inflammation. Joints are places where two bones meet, such as your elbow or knee. There are many different types of arthritis with different causes and treatments. In some types, other organs, such as your eyes, heart, or skin, can also be affected. Common symptoms of arthritis include pain, redness, heat, and swelling in your joints. If you have arthritis, it is important for your doctor to diagnose the type of arthritis you have so that you can get the proper treatment. Fortunately, current treatments allow most people with arthritis to lead active and productive lives.

2. MATERIALS AND METHOD-

Material-

1. Active Pharmaceutical Ingredient (API):

Meloxicam (99 % purity) was purchased from Cerata Pharmaceuticals LLP, Surat, India. It cost around 3700 rupees per kg. This is the core ingredient, the actual medication that delivers the therapeutic effect. [11]

2. Release-controlling polymers:

Hydrophilic polymers: Hydroxypropyl methylcellulose (HPMC) were purchase from chemical store of Shivajirao Pawar College of Pharmacy. They are useful to form a matrix or coating that regulates the rate at which the drug dissolves and releases from the tablet. [12]

3. Excipient:

All excipient were purchased from the chemical store of Shivajirao Pawar College of Pharmacy.

- Fillers: Lactose. These make up the bulk of the tablet and provide structure.
- Disintegrants: Sodium starch glycolate. These help the tablet break apart after ingestion, allowing for faster drug release.
- Lubricants: Magnesium stearate. These prevent sticking during tableting and ensure smooth passage down the throat.
- Glidants: Talc (pharmaceutical grade). These improve powder flow during manufacturing.
- Solvents: Ethanol.
- Sweeteners or flavorings: Mannitol. Used to improve palatability. [13,14]

Method for preparation of sustained release tablet-

Sustained release tablet, each tablet containing 8-15 mg Meloxicam were prepared by conventional wet granulation method. [15] The composition of various formulations of the sustained release tablets with their taken quantity is shown in Table 1. In each formulation the quantity of active pharmaceutical ingredient is 8-15 mg and the total weight of tablet is 100

mg. Total 10 tablet was prepared with each formula. Formulation was done by following steps of method. [16]

- **Sieving:** All ingredients are passed through a 60-mesh sieve to ensure a uniform particle size.
- **Blending and Mixing:** Except for the glidant and lubricant (which will be added later), all the ingredients are blended and mixed thoroughly.
- **Wet Granulation:** A water or methanol solution is used to bind the powder particles together and form wet masses. This is done manually.
- **Sieving and Drying:** The wet masses are passed through a 12-mesh sieve to create granules of a specific size. These granules are then air-dried for 10 minutes, followed by final drying in a tray dryer at 45-50°C for 2 hours.
- **Sizing and Lubrication:** The dried granules are passed through a 16-mesh sieve to achieve the desired final size. Then, magnesium stearate, a lubricant, is added to improve flow during tableting.
- **Tablet Compression:** The lubricated granules are compressed into tablets using a tablet compression machine with a constant compression force. Before compression, the machine's die and punches are also lubricated with magnesium stearate to prevent sticking.
- **Storage:** The finished tablets are stored in airtight containers for further testing or use.

Table 1. Composition of sustained release tablet formulation- [17,18]

Ingredients	Formula 1 (mg)	Formula 2 (mg)	Formula 3 (mg)
Meloxicam	12	15	8.5
Release-controlling polymers	4	3.5	3.9
Fillers	80	75	78
Disintegrants	1.3	1.5	1.8
Lubricants	0.14	0.16	0.13
Glidants	0.12	0.14	0.16
Solvents	q.s	q.s	q.s
Sweeteners or flavorings	q.s	q.s	q.s

Evaluation test for granules- Granule evaluation is a crucial step in the tableting process, ensuring the granules possess the characteristics necessary for forming good quality tablets. Here are some common tests performed on granules: [19,20,21]

Angle of Repose- This test measures the angle formed by a pile of granules when poured freely. A steeper angle indicates poor flow, while a shallower angle indicates good flow. The angle of repose (θ) was calculated as follows:

- Angle of Repose (θ) = $\tan^{-1}$ (2h / d)

Bulk Density and Tapped Density- Both bulk density and tapped density are important for understanding the behavior of powders and granules in tableting processes. Here are the formulas for each:

- Bulk Density (ρb): M / V
- Tapped Density (ρt): M / Vf

Compressibility Index and Hausner Ratio- The Compressibility Index and Hausner Ratio are both calculated using the values of bulk density (ρb) and tapped density (ρt) obtained from the formulas you saw earlier. Here's how they are related:

- Compressibility Index (CI): 100 * (ρt - ρb) / ρb
- Hausner Ratio (H): ρt / ρb

Evaluation test for tablet- [22,23]

NON-OFFICIAL TEST

Organoleptic property- The organoleptic properties of a tablet refer to the sensory attributes perceived by the consumer upon consumption. These properties include parameter like color uniformity, odor, texture and taste.

Size and Shape- A size and shape evaluation test are a routine quality control procedure performed on tablets during manufacturing. For thickness, a tolerance of ±5% deviation from the standard value is generally considered acceptable. This ensures consistent tablet weight and drug delivery. Shape is evaluated visually to confirm it matches the intended design, such as round.

Hardness Test- This testing plays a vital role in maintaining the quality and consistency of pharmaceutical tablets. This test done by using Monsanto hardness tester. Tablet Crushing

Strength/Hardness: all tablet passed a test to measure their resistance to breaking under pressure. Acceptable Range: The crushing strength for all tablet fall within an acceptable range of 5kg/cm² to 10kg/cm².

Friability- It is an important quality control procedure in the pharmaceutical industry that evaluates a tablet's resistance to chipping, cracking, or breaking under physical stress during handling, transportation, and storage. Friability test was done by using rochefriabilator. The friability is expressed as a percentage of the weight lost compared to the initial weight of the sample. Each tablet formulation typically has a predefined acceptable friability limit (usually less than 1%).

OFFICIAL TEST-

Weight Variation Test (U.S.P.)- This test ensures that the weight of individual tablets within a batch is consistent. This consistency is important for maintaining accurate medication dosing.

Content uniformity- Content uniformity of a tablet refers to the consistency of the active pharmaceutical ingredient (API) or multiple APIs within individual tablets, as well as across a batch of tablets. It ensures that each tablet in a batch contains the specified amount of active ingredients and meets the required quality standards.

Disintegration test- It helps to know about the solubility of active pharmaceutical ingredient in gastric fluid of digestive system. This disintegration rate is essential for ensuring proper drug release and absorption in the body. This test is done by using tablet disintegration machine.

Dissolution test- This test is essential for the measurement of rate and extent of drug release form the tables (under standardized condition of temperature and solvent composition) is estimated by basket dissolution test apparatus.

4. RESULTS AND DISCUSSION-

The meloxicam granules were prepared and formulation of sustained release meloxicam tablet were done also evaluated for various parameter and average of results of three formulas are shown in following table 2 evaluation of meloxicam granules and table 3. evaluation of meloxicam tablet.

Table 2. Evaluation of meloxicam granules.

Test	Observational values	Standard values
Angle of repose (^{0})	33	25±5
Bulk density (g/cm^3)	0.7	0.5±3
Tapped density (g/cm^3)	0.82	1±5
Hausner ratio	1.71	1.10±5
Carr's Index (%)	14	10±5

Table 3. Evaluation of meloxicam tablet.

Test	Observational values	Standard values
Color	Milky white	-
Odor	Odourless	-
Texture	Smooth	-
Size and Shape	Round off	-
Hardness Test (kg)	4.3	6±3
Friability (%)	1.19	Not more than1
Weight Variation (%)	4	Not more than5
Content uniformity	93 %	95±2 %
Disintegration test min	45	10±5
Dissolution test(min)	67	80 %

All the prepared formulations passed or having nearby observational values as compared to standard values. The values of angle of repose, bulk density, tapped density, hausner ratio and carrs index shows that meloxicam granules have good flowability. Table 3. Shows that the all

meloxicam tablet has good hardness, low friability, also disintegrate and statistically dissolve in standard medium.

5. CONCLUSION-

Meloxicam, a widely used non-steroidal anti-inflammatory drug (NSAID) for arthritis treatment, suffers from a short half-life necessitating frequent dosing and potentially hindering

patient compliance. This study successfully formulated sustained release meloxicam tablets using HPMC as the release-retarding polymer. By optimizing the HPMC grade and formulation composition, a desired drug release profile can be achieved, potentially improving patient compliance and therapeutic outcomes in arthritis treatment. Further in-vivo studies are necessary to evaluate the efficacy and safety of the formulated tablets in animal models or clinical trials.

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REFERENCE-

1. Noble, s., & balfour, j. A. (1996). Meloxicam. Drugs, 51(3), 424–430. Https://doi.org/10.2165/00003495-199651030-00007

2. Wikipedia contributors. (2024, may 4). Meloxicam. Wikipedia. Https://en.wikipedia.org/wiki/meloxicam
3. Pubchem. (n.d.). Meloxicam. Pubchem. Https://pubchem.ncbi.nlm.nih.gov/compound/meloxicam
4. Fleischmann, r., iqbal, i., & slobodin, g. (2002). Meloxicam. Expert opinion on pharmacotherapy, 3(10), 1501–1512. Https://doi.org/10.1517/14656566.3.10.1501
5. Yasmeen, r., asif, l., & djeffal, s. (2021). Impact of diclofenac a non-steroidal anti-inflammatory veterinary pharmaceutical drug on vultures. Pakistan journal of zoology, 54(1). Https://doi.org/10.17582/journal.pjz/20191121081106
6. Türck, d., roth, w., & busch, u. (1996). A review of the clinical pharmacokinetics of meloxicam. Rheumatology, 35(suppl 1), 13–16. Https://doi.org/10.1093/rheumatology/35.suppl_1.13
7. Khalil, n. Y., & aldosari, k. F. (2020). Meloxicam. In profiles of drug substances, excipients, and related methodology (pp. 159–197). Https://doi.org/10.1016/bs.podrm.2019.10.006
8. Gates, b. J., nguyen, t. T., setter, s. M., & davies, n. M. (2005). Meloxicam: a reappraisal of pharmacokinetics, efficacy and safety. Expert opinion on pharmacotherapy, 6(12), 2117–2140. Https://doi.org/10.1517/14656566.6.12.2117
9. Luger, p., daneck, k., engel, w., trummlitz, g., & wagner, k. G. (1996). Structure and physicochemical properties of meloxicam, a new nsaid. European journal of pharmaceutical sciences, 4(3), 175–187. Https://doi.org/10.1016/0928-0987(95)00046-1
10. Firestein, g. Evolving concepts of rheumatoid arthritis. Nature 423, 356–361 (2003). Https://doi.org/10.1038/nature01661
11. Kumar, v., bansal, v., madhavan, a., kumar, m., sindhu, r., awasthi, m. K., binod, p., & saran, s. (2022). Active pharmaceutical ingredient (api) chemicals: a critical review of current biotechnological approaches. Bioengineered, 13(2), 4309–4327. Https://doi.org/10.1080/21655979.2022.2031412
12. Liechty, w. B., kryscio, d. R., slaughter, b. V., & peppas, n. (2010). Polymers for drug delivery systems. Annual review of chemical and biomolecular engineering, 1(1), 149–173. Https://doi.org/10.1146/annurev-chembioeng-073009-100847
13. Van der merwe, j., steenekamp, j., steyn, d., & hamman, j. H. (2020). The role of functional excipients in solid oral dosage forms to overcome poor drug dissolution and

bioavailability. Pharmaceutics, 12(5), 393. Https://doi.org/10.3390/pharmaceutics12050393

14. Chakraborty, tapamoy. (2022). Tablets preparation, excipients and tests.
15. Suzuki, y., sugiyama, h., kano, m., shimono, r., shimada, g., furukawa, r., mano, e., motoyama, k., koide, t., matsui, y., kurasaki, k., takayama, i., hikage, s., katori, n., kikuchi, m., sakai, h., & matsuda, y. (2021). Control strategy and methods for continuous direct compression processes. Asian journal of pharmaceutical sciences, 16(2), 253–262. Https://doi.org/10.1016/j.ajps.2020.11.005
16. Wadher, k., kakde, r., & umekar, m. J. (2011). Formulation and evaluation of a sustained-release tablets of metformin hydrochloride using hydrophilic synthetic and hydrophobic natural polymers. Indian journal of pharmaceutical sciences/indian journal of pharmaceutical sciences, 73(2), 208. Https://doi.org/10.4103/0250-474x.91579
17. Burke, m. H., & individual. (2007, december 19). Gb2455875a - meloxicam tablet formulations and their preparation - google patents. Https://patents.google.com/patent/gb2455875a/en
18. Yang, z., liu, l., sheng, l., wang, h., li, c., xia, l., & yang, p. (2024). Design of an injectable sustained release in-situ forming depot of meloxicam for pain relief. Journal of drug delivery science and technology, 93, 105460. Https://doi.org/10.1016/j.jddst.2024.105460
19. Chaturvedi, h., garg, a. And rathore, u.s., 2017. Post-compression evaluation parameters for tablets-an overview. Eur j pharm med res [internet], 4(11), pp.526-30.
20. Shah, r. B., tawakkul, m. A., & khan, m. A. (2008). Comparative evaluation of flow for pharmaceutical powders and granules. Aaps pharmscitech, 9(1), 250–258. Https://doi.org/10.1208/s12249-008-9046-8
21. Szumiło, m., belniak, p., świąder, k., holody, e., & poleszak, e. (2017). Assessment of physical properties of granules with paracetamol and caffeine. Saudi pharmaceutical journal, 25(6), 900–905. Https://doi.org/10.1016/j.jsps.2017.02.009
22. Mohdazam, neha sodiyal , sivanandpatil. A review on evaluation of tablet. International journal of research in engineering and science (ijres) volume 10 issue 4 ǁ 2022 ǁ pp. 79-82
23. Rastogi, trapti & khadabadi, s. (2011). Design, development and evaluation of matrix tablet containing indigenous medicinal plants. International journal of pharmaceutical sciences and research. 2.

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