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Formulation and Evaluation of Extended-Release Tablets of Etodolac

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HUMAN

Neha Rawat*[1], Shalini Singh[2], Abadhesh Kumar Niranjan[3], Bushra Jabi[4]

1. Research Scholar, Institute of Pharmaceutical Science and Research, Unnao, U.P. India.

2. Associate Professor, Institute of Pharmaceutical Science and Research, Unnao, U.P. India.

3. Associate Professor, Hygia Institute of Pharmaceutical Education and Research, Lucknow, U.P. India.

4. Ph.D Scholar, Faculty of Pharmacy, Jamia Hamdard University, New Delhi, India.

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ABSTRACT

The most widely recognized course is the oral medication release strategy. Physical characteristics of drugs, polymers, and excipients were described, including the angle of repose, density, compressibility index, Hausner's ratio, etc. Different etodolac particle sizes were used in the formulation of the etodolac tablets in the current investigation. The range of formulations' mean particle sizes (effective diameters) was 46.90.358 nm to 1043.3510.2 nm. Because Etodolac is a lipophilic molecule, its low aqueous solubility was constant over the physiological pH range. A friabilator was filled with a pre-weighed sample of tablets, and it was rotated 100 times. The range of hardness was 4.9% to 5.7%. Friability was between 0.1 and 0.5. The examined parameters before and after the formulations had been aged in storage did not significantly differ from one another; all were found to be within acceptable limits. To develop an extended-release formulation for the selected etodolac drug using polymers such as pharmaceutical for Tablet formulations. This project would be useful for bringing relief to a large population suffering from inflammation and its uses for different causes.

INTRODUCTION

Pharmaceutical drug

In pharmacology, a medication is a synthetic compound, generally one with a notable design, that, when given to something living, has a natural effect. [1] A drug is a synthetic compound that is utilized to treat, fix, forestall, or analyze a disease, as well as to further develop prosperity. It is otherwise called a drug or medication. Previously, prescriptions were separated from restorative plants, however, as of late, they were likewise made naturally. [2] Pharmaceutical meds for constant sicknesses might be taken incidentally or for a short timeframe. [3]

Drug meds are regularly gathered into drug classes, which are made out of medications that are utilized to treat a similar condition and have practically identical compound designs, and a similar component of activity (restricting to the equivalent natural target).[4,5] The most famous medication characterization framework, the Anatomical Therapeutic Chemical Classification System (ATC), gives each medication an extraordinary ATC code, an alphanumeric identifier that puts the medication in one of the framework's assigned medication classes. The Biopharmaceutics Classification System is another significant grouping plan. As indicated by their solvency and porousness, or retention, characteristics, this arranges meds. [6]

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Biopharmaceutics Classification System is another significant grouping plan. As indicated by their solvency and porousness, or retention, characteristics, this arranges meds. [10]

Oral drug delivery

Due to benefits like the simplicity of oral medication organization, patient inclination, cost viability, and the straightforwardness of creating oral measurement structures on a wide scale, oral medicine is the most famous strategy for a drug organization. The oral course of the organization is utilized to control around 60% of laid-out little particle restorative items that are financially open. As per current gauges, the worldwide portion of the overall industry for everything drug plans intended for human use is held by oral definitions to a level of generally 90%. Orally controlled drugs make up around 84% of the top-selling meds, which are presently esteemed at $35 billion and developing at a 10% yearly rate. [11] Patients are commonly more agreeable with oral definitions for asthma drugs than they are with elective parenteral strategies including intravenous, subcutaneous, and intramuscular infusions. For the restricted therapy of neurotic circumstances like the stomach and colorectal tumors, contaminations, irritations, entrail sicknesses, gastro-duodenal ulcers, and gastroesophageal reflux issues, orally managed drugs can likewise be coordinated to explicit regions inside the gastrointestinal (GI) plot. [12,13]

Advantages of oral controlled release systems:[14]

When used therapeutically, it lessens medication plasma level fluctuations and keeps.

- a constant plasma level for the allotted duration.
- Reduction of negative effects – Negative effects typically appear when a medicine exceeds its therapeutic or hazardous limit. Typically, this occurs with traditional dose forms. The drug therapeutic window is maintained through regulated administration.
- Reducing side effects is also a result of reducing drug quantity through CR design.
- A decrease in dosage frequency might address patient issues
- For improved in vivo tolerance of some medications, such as Rivastigmine tartrate
- It's economical.

Ideal characteristics of drugs to design as controlled drug delivery[15]

- The drug's half-life should be between 2 and 8 hours.
- Medicines have a broad therapeutic index.
- Medications that demand improved bioavailability.
- Less than 1gm of the medicine should be placed into the dosage form.
- Disease conditions that call for regulated release.
- Cost savings are brought on by a general decrease in medication dosage.
- Medicines that have side effects when used in conventional therapy.
- Instead of requiring a specific dose for each patient, the treatment must be effective at a common dose for a bigger group.

Extended-release tablets

Expanded discharge drugs work by leisurely delivering their dynamic fixings into the body for more than a few hours or days. Generally, they come as an oral tablet or an oral container. They contrast with drugs with quick delivery, which begins working soon after utilization. Expanded discharge drugs are those whose pace of medication discharge is constrained by a particular covering, layer injected with the medication, case with a novel opening, container containing remarkable dots, or hard-to-break-up tablet. A few items join multiple ways of conveying drugs at the ideal rate. Stretched-out discharge pills are intended to keep up with your measurement at consistent levels for longer timeframes and are commonly utilized once every day. They are oftentimes recommended to patients whose meds are not filling in as well as they ought to. Broadened discharge drugs should be taken precisely as coordinated. While utilizing broadened discharge medications, pills or containers ought not to be squashed, split, or orbited. If a prescription expected for broadened discharge is squashed or eaten, it might cause an excess. Solution bottles should be kept fixed and in a dry area since air or dampness can modify the detailing's viability. A medication for broadened delivery might lose a portion of its viability if its underlying structure is changed. [16]

Advantages of Extended release tablets [18]

Extended-release drugs have several benefits, including but not limited to the following:

- Less regular dosages
- Less negative consequences
- Blood levels fluctuate less.
- Total assimilation

Evaluation of Drug

Physical characteristics of drugs, polymers, and excipients were described, including the angle of repose, density, compressibility index, Hausner's ratio, etc.[19-21]

Particle size determination

Different etodolac particle sizes were used in the formulation of the etodolac tablets in the current investigation. The Malvern approach was used to calculate the particle size. A sample of dispersed etodolac was run through the optical bench's measuring section, where the laser beam illuminates the particles and the intensity of the light reflected by the detectors is used to calculate the size of the particles.[22-24]

Angle of Repose

The funnel method was used to calculate the angle of repose. The carefully measured powder was put into a funnel. The funnel's height was adjusted such that the tip of the device just brushed the peak of the powder heap. The funnel was left open, letting the powder freely pour out onto the ground. The powder cone's diameter was measured.[25,26]

The following equation was used to get the angle of repose.

$$\tan(\theta) = h/r$$

Where ‘h’ and ‘r’ are the height and radius respectively of the powder cone.

Table 1 Standard values of angle of repose (θ)

Flowability	Angle of repose
Excellent	25-30
Good	31-35
Fair	36-45
Poor	45-55
Very poor	56-65
Very very poor	>66

Bulk Density

similar loose bulk densities (LBD). A graduated measuring cylinder was filled with a predetermined quantity of granules from each formula that had been previously lightly agitated to break any agglomerates that may have formed. After the initial volume was measured, the cylinder was allowed to drop under its height at intervals of two seconds onto a hard surface. These formulas were used to determine LBD. After carefully levelling, the powder and noting any disturbed apparent volume, the apparent bulk density in g/ml was determined using the formula below:[27,28]

LBD= Weight of the powder/volume of the packing

Determination of tapped bulk density

A precise dosage of the medicine was consumed; it had earlier been put into a 100 ml graduated cylinder after passing through a 20 # sieve. Then, using a mechanically tapped density tester that produces a set drop at a nominal rate of 300 drops per minute, the cylinder containing the sample was mechanically tapped by elevating and allowing it to fall under its weight. The cylinder was originally tapped 500 times, and the tapped volume (V1) was measured to the nearest graduated units. The tapping was then done an additional 750 times, and the tapped volume (V2) was measured to the nearest graded units. The final volume (V2) 83 was taken if the difference between the two volumes was less than 2%.[29,30]

TBD= Weight of the powder/tapped volume of the packing

Compressibility Index

Carr's compressibility index, which was derived using the formula below, was used to determine the compressibility index of the granules:[31]

$$\text{Carr's index (\%)} = [(TBD-LBD)\times 100]/TBD$$

Hausner's Ratio

Hausner discovered that the DF/DO ratio was associated with interparticle friction and could therefore be utilized to forecast powder flow characteristics110. The formula below is used to calculate it:[32]

$$\text{Hausner's ratio} = DF/DO$$

where DF has Tapped bulk density and DO is Loose bulk density.

Table 2 Standard values of Carr's index and Hausner's ratio

Type of flow	Carr's index	Hausner's Ratio
Excellent	<10	1.00-1.11
Good	11-15	1.12-1.18
Fair	16-20	1.19-1.25
Passable	21-25	1.26-1.34
Poor	26-31	1.35-1.45
Very poor	32-38	1.46-1.59
Very, Very poor	>38	>1.60

Solubility determination

By evaluating Etodolac's solubility in various solvents, solubility was examined.:

1) Purified water
2) 0.1 N Hydrochloric acid (HCl), USP
3) Phosphate buffer of pH 6.8, USP

4) Phosphate buffer of pH 7.4, USP

10 mL of the aforementioned media were added to a conical flask at a temperature of 37 0.5 ^{o}C. The above conical flask was filled with previously weighed amounts of the active substance until the saturation point was reached. It was noted how much medication was added in total. Stirring was kept for 24 hours at 37 0.5 degrees Celsius.

Using a 0.45 m filter, the material was purified. The filtered material was measured out and put into another volumetric flask where more dilutions were prepared. Each buffer medium's Etodolac concentration was calculated.

Preparation of powders-mix

The Etodolac pills were made utilizing a granulation strategy. As a diluent, lactose monohydrate was utilized. The grinding specialist was a 15% w/w arrangement of polyvinylpyrrolidone (PVP) in refined water. Setting up the Binder Solution: In a reasonable vessel with a stirrer, the important measure of cleansed water was added to accomplish a 15% w/w cover fixation. PVP was progressively added to the sifted water while being mixed, bringing about an unmistakable arrangement. The rate retardant substance (Polymer), trehalose dihydrate, and precisely weighed unadulterated drug were hand mixed for 10 minutes before being figured out ASTM#20 network. This dry combination was joined with the fastener arrangement, and the subsequent wet mass was gone through an ASTM #18 cross-section to deliver consistently estimated granules. The wet granules were dried in a plate dryer at a temperature of 45 5 °C until a misfortune on drying worth of NMT 1.0% w/w was reached (at 60 °C utilizing auto mode IR dampness analyzer). Dried granules were moved to a polyethylene sack after being arranged to utilize an ASTM #25 lattice.

To create 9 kilogram, 12 kg, and 15 kg hard tablets, the obtained powder mixture was divided into three batches. Each batch was compressed using a manual tablet press that had flat-faced tooling with dimensions of 83.5 mm. The resulting tablets were each 100 mg.

Table 3 Etodolac Formulation Table

Formulation	Fme-1	Fme-2	Fme-3	Fme-4
Etodolac	10	10	10	10
PVP	15	14	15	14
Magnesium stearate (%)	2	3	2	3
Lactose Monohydrate	25	25	25	25
Methanol	20	15	20	15
Distilled water	15	20	15	15

Evaluation of tablets

The following qualities were assessed in the prepared tablets:

Thickness and diameter

The uniformity of the weight was assessed using a random sample of 20 tablets. An electronic digital balance was used to weigh each of the 20 tablets both collectively and individually. Determined where the mean and % deviations were.

Digital vernier callipers were used to measure the thickness of six tablets from each batch, and the results were given in millimeters (mm). Average values and standard deviations were computed and reported using all of these individual values.

To achieve the requisite uniformity in size and shape, the diameter of the tablets was precisely measured using a digital Vernier calliper.

Hardness

The strength of a tablet is determined by how hard it is. By measuring the amount of force needed to break the tablet across its circumference, it is put to the test. The hardness is expressed in kilograms (kg), and 4 kg is thought to be sufficient hardness for uncoated tablets. For this, a Monsanto hardness tester is employed. Six pills were tested for hardness, and the average hardness was determined.

Friability test

The loss of weight of tablets in a container due to the removal of small particles from their surfaces is known as friability. The friability test evaluates the tablet's resistance to abrasion during handling, packing, and transportation. The tablet's friability was evaluated using an Electrolab friability tester. Six (6) tablets were weighed precisely and put inside the device's chamber. The tablets were removed from the device after 100 spins, dusted again, and weighed. The weight loss reveals the pills' brittleness. Tablets can have a maximum friability of 1%, according to the Indian Pharmacopoeia (IP). The algorithm below was used to calculate the percentage of friability:

$$\% \text{ friability} = (W1 - W2 / W1) \times 100$$

Where,

W1 = weight of tablets before a test

W2 = weight of tablets after the test

Uniformity of weight

20 tablets were chosen at random, cleaned, and then each one was weighed. The following was used to calculate the percentage of weight variance from the tablet's real average weight:

% weight variation from actual average weight of tablet = [100 x ((Individual tablet weight – Average weight)]/Average weight of tablet

Acceptance criteria: If no more than two tablets fall outside the permitted percentage range and no tablet deviates by a margin greater than twice the permitted range, the tablet passes the test. According to Ph. Eur, the following weight variation percentage variance is permitted.

Table 4 Weight variation limit as per the average weight of tablet (Ref. Ph. Eur.)

S.no	Average weight of a tablet	Percentage deviation
1.	**80 mg or less**	**10%**
2.	**More than 80 mg, less than 250 mg**	**7.5%**
3.	**250 mg or more**	**5%**

Dissolution Testing:

Utilizing an autosampler, the produced tablets were assessed for in-vitro drug release tests. The following circumstances govern how core pills dissolve. The gathered findings are summarised and utilized to choose the optimal formulation. The outcomes for etodolac were listed in the table below.

Stability studies as per the ICH guidelines [33]

As required by the International Conference on Harmonization (ICH)105, developed SR tablets were placed in High-Density Poly Ethylene (HDPE) containers and submitted to stability testing at the following varying temperatures and humidity levels.

- 25°C with 60 % RH
- 40°C with 75 % RH

The values will be taken into account in the context of the current situation; a little discrepancy may exist in terms of absolute numbers but not proportions. The facts will speak to the state of the development strategy along with a sincere concern for the welfare of the suffering human.

Preformulation studies

Particle size determination

Etodolac's particle size may have an impact on both in vivo performance and in vitro dissolution. Malvern particle size analyzer was used to measure the particle size distribution of three different lots of etodolac. The range of formulations' mean particle sizes (effective diameters) was 46.90.358 nm to 1043.3510.2 nm. The findings are displayed in Table 5.1:

Table 5 Particle size determination

Evaluation Parameters	Particle Size(nm)
Fme-1	515
Fme-2	225
Fme-3	345
Fme-4	561

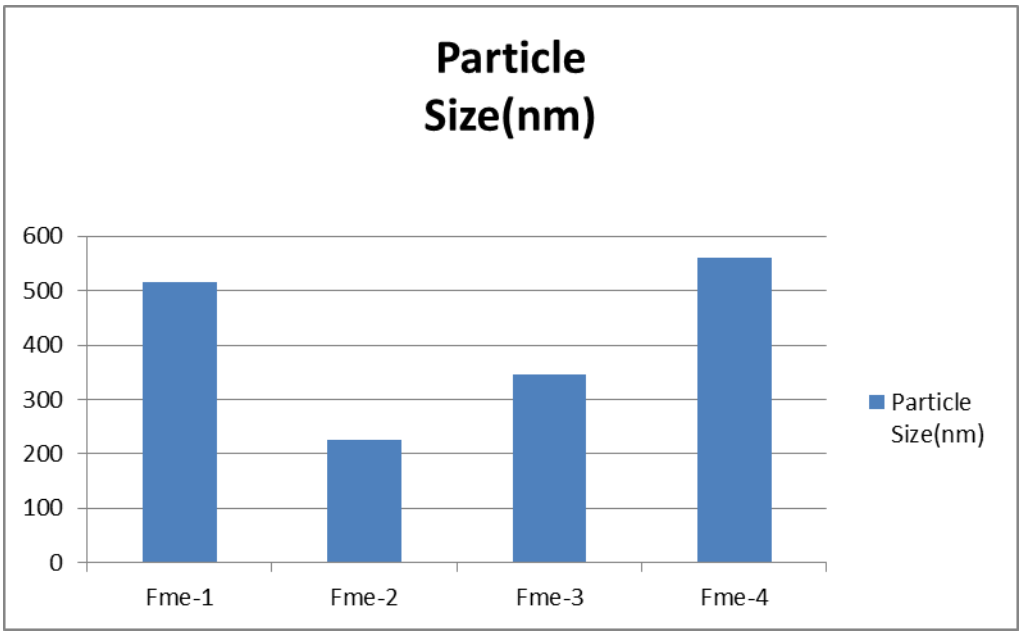

Figure 1 Particle Size(nm) graph

Solubility Study of Etodolac

Because Etodolac is a lipophilic molecule, its low aqueous solubility was constant over the physiological pH range. Etodolac is classified as a weakly soluble pharmacological substance based on its solubility throughout a range of physiological pH levels, which is supported by both experimental and literary evidence.

Table 6 Solubility data of Etodolac in various buffers:

Medium	Solubility (mcg/ml)
1.2 pH buffer	101
6.8 pH buffer	20
Purified water	140
Hydrochloric acid	200

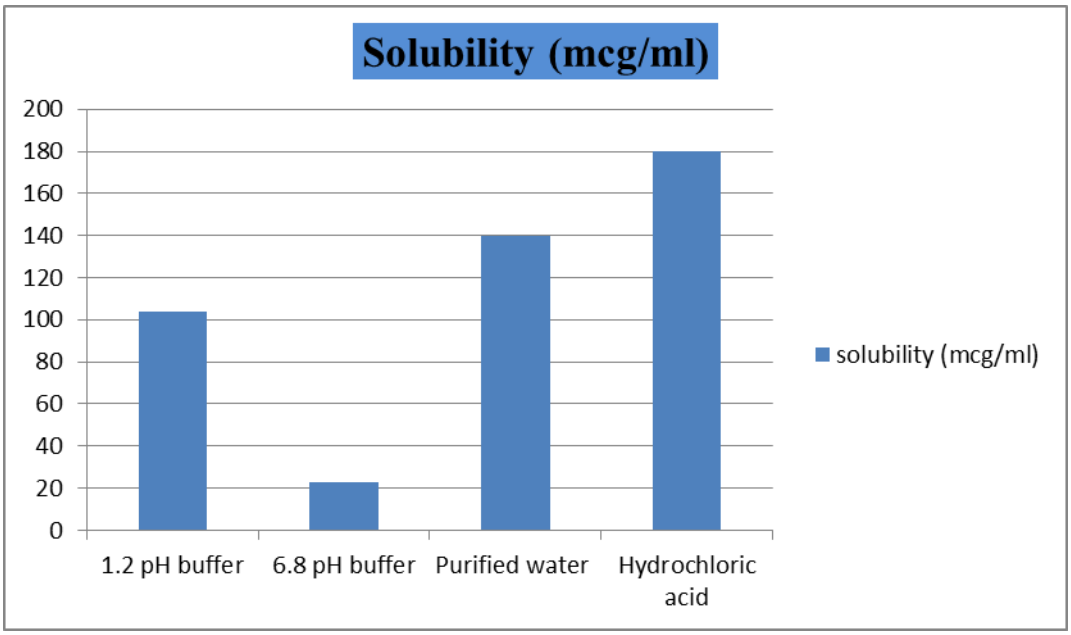

Figure 2 Solubility (mcg/ml) graph

Evaluation of granulations

Granulation, which includes the nonstop arrival of a prescription from covered or lattice-type particles, is the significant cycle in the formation of various measurement structures. A gathering of independent particles connected by bonds with a limited strength is alluded to as a granule. Even though network tablets could have been delivered utilizing an immediate pressure procedure, wet granulation (non-watery) is ideal in run-of-the-mill business assembling to accomplish sufficient substance homogeneity and take out stream related between tablet weight variety process. The current examination thus utilized the wet granulation process. Drugs consolidated in heterogeneous detailing can break up at various

rates relying upon the actual qualities of the granules, like size, shape, hardness, surface qualities, and explicit surface region. Point of rest, free mass thickness (LBD), tapped mass thickness (TBD), Carr's record (CI), and Hausner's proportion was estimated in the granules of therapeutic plans (HF). The tablets beneath show the outcomes that were gotten. The previously mentioned strategy couldn't decide the point of rest for etodolac powders. The powder was too strong to even think about going through the pipe, however, Etodolac granules had a point of rest esteem that went from 21.99° to 23.70°.

The delivered Etodolac granules' Hausner's proportion values went from 1.154 to 1.348. The last option was accepted to be demonstrative of the made granules' positive stream qualities because of the granulation-actuated expansion in molecule size. Furthermore, because of a relative expansion in molecule size when contrasted with untreated powder, granulation has diminished the tapping thickness. Carr made a technique to gauge the capacity of powder to move from mass densities called % compressibility.

Etodolac's % compressibility was found to be 54.05. The suspicion that granulation expanded both stream capacity and compressibility was upheld by this finding, which was as per the aftereffects of point of rest and HF. It was found that Etodolac's granules contained a minimal measure of fines conceivable. The moment discharge powder blend showed great stream qualities (Angle of rest more than 27 and under 30). The results showed that a powder mix for guaranteed delivery could be straightforwardly squashed into tablets.

Table 7 Evaluation of granulationspre-compression studies:

Evaluation Parameters	**Bulk density (g/cc)**	**Hausner`s ratio**	**Tapped density (g/cc)**
Fme-1	0..54	1.18	0.64
Fme-2	0.50	1.16	0.58
Fme-3	0.52	1.15	0.60
Fme-4	0.46	1.19	0.55

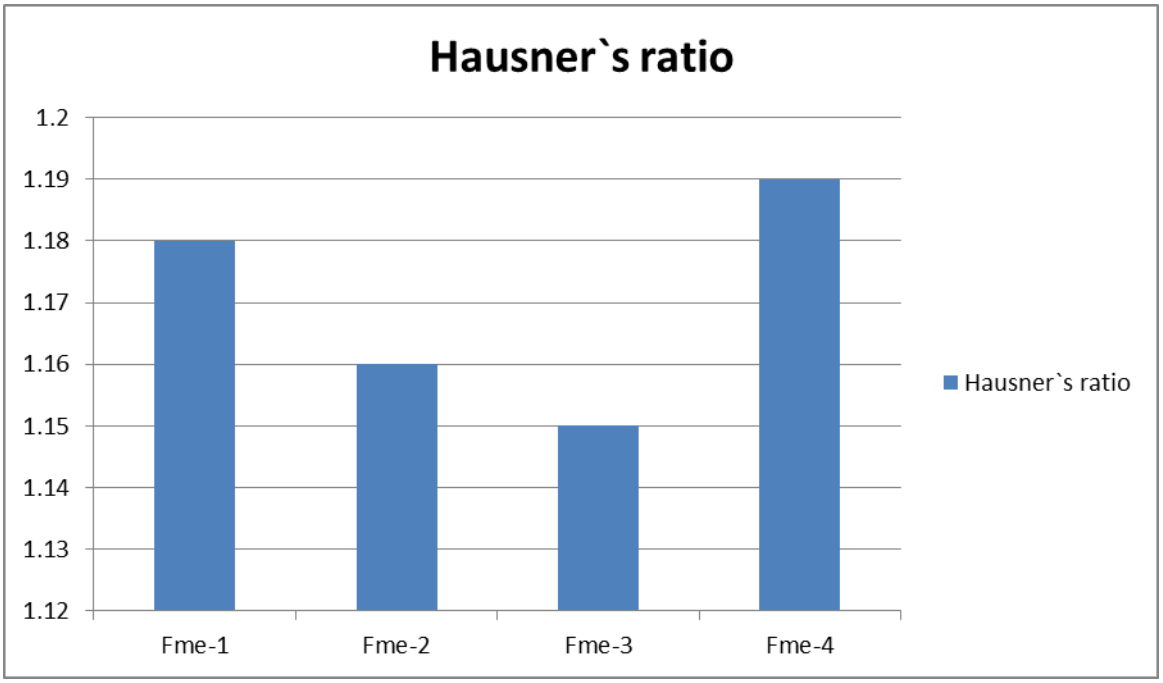

Figure 3 Graph of Granules pre-compression studies

Table 8 Evaluation of granulations pre-compression studies

Evaluation Parameters	Compressibility index (%)	Angle of repose (θ)
Fme-1	9.36	21.74
Fme-2	13.70	20.12
Fme-3	13.22	23.36
Fme-4	16.34	21.08

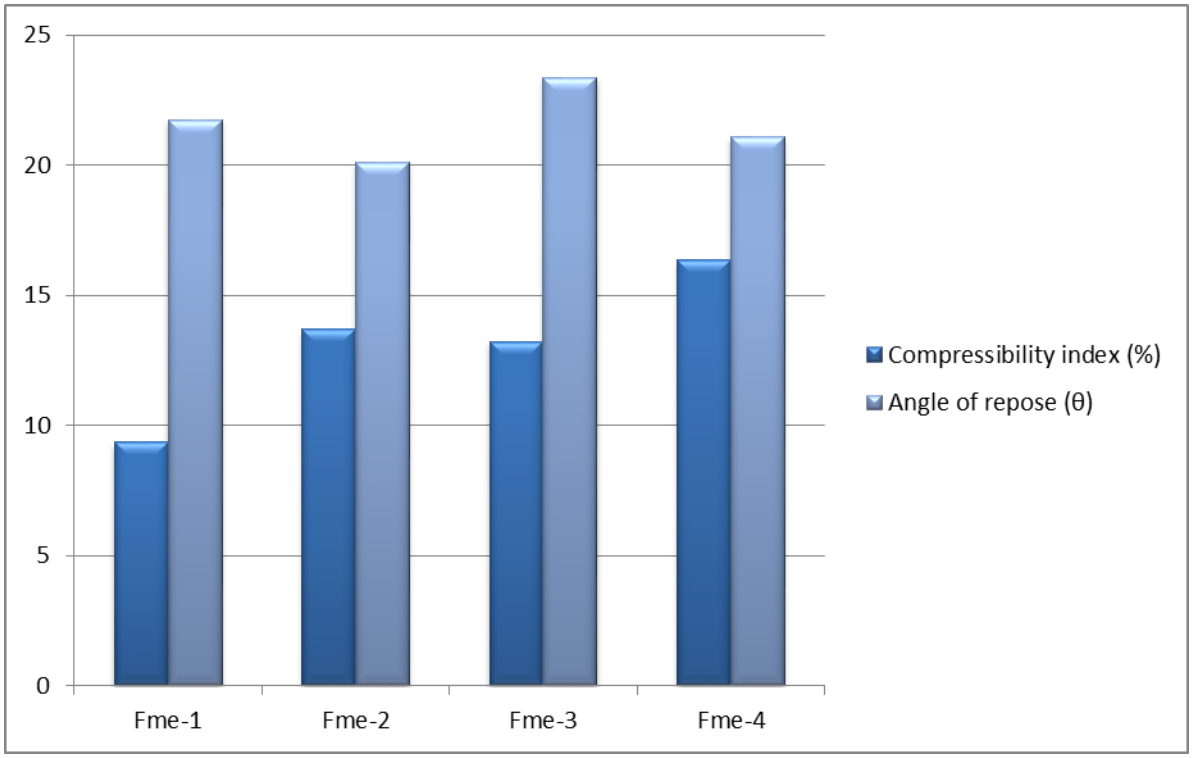

Figure 4 Graph of pre-compression studies

Determination of Parameters of a drug (post-compression studies)

By turning the screw knob forward, the force being exerted on the tablet's edge is steadily increased until the tablet breaks. The scale's reading, which expresses the amount of pressure needed to break tablets in kilograms per square meter, is reported. A friabilator was loaded with a pre-weighed sample of tablets, and it was rotated 100 times.

Table 9 Evaluation Parameters of the formulation

Evaluation Parameters	Hardness (%)	Friability (%)	Drug Content(%)
Fme-1	4.9	0.3	92.35
Fme-2	5.1	0.5	91.46
Fme-3	5.7	0.3	92.64
Fme-4	5.3	0.4	90.35

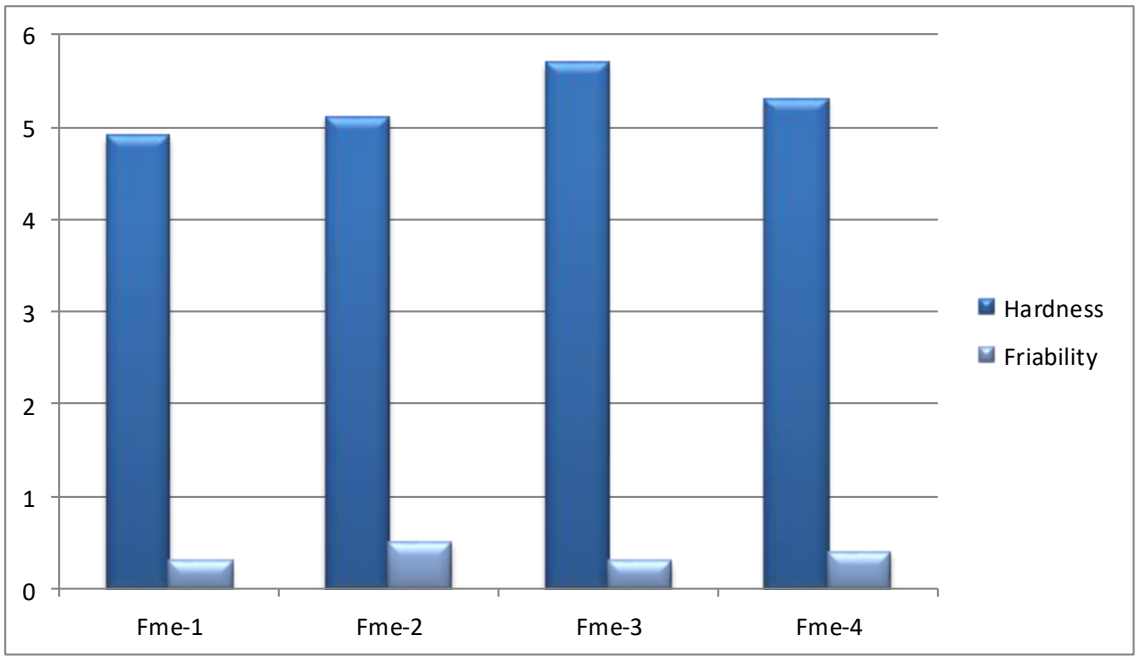

Figure 5 Graph of Evaluation Parameters of the formulation

Table 10 Evaluation Parameters of the formulation

Evaluation Parameters	Thickness (mm)
Fme-1	2.1
Fme-2	2.5
Fme-3	2.3
Fme-4	2.4

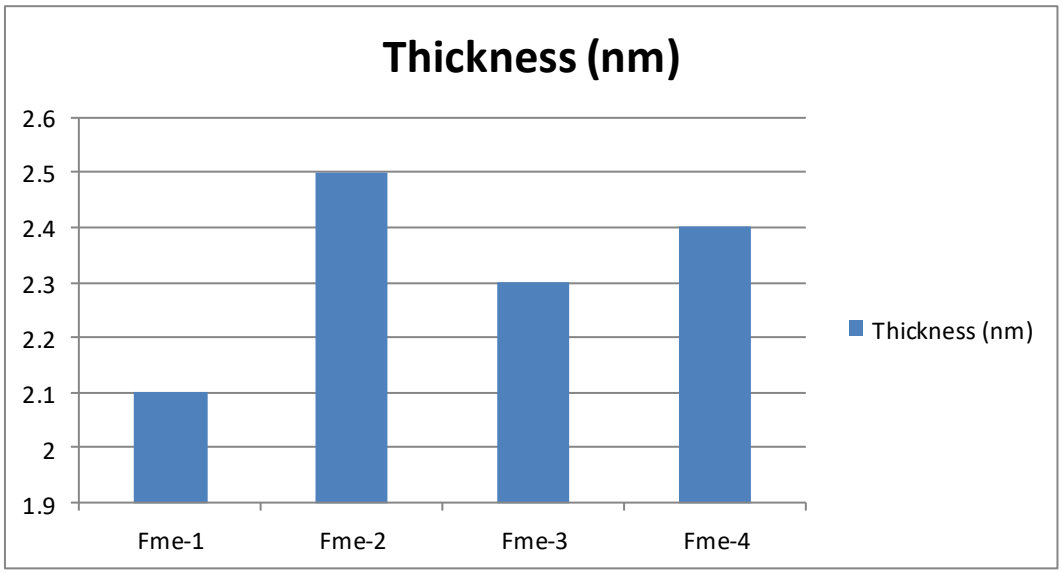

Figure 6 Thickness (nm) graph

Table 11 Dissolution data of optimized batches of tablets in 6.8 pH buffer.

Evaluation Parameters	Time (min) 0	Time (hour)1	Time (hours) 4	Time (hours)24
Fme-1	0	68.45	76.35	79.15
Fme-2	0	69.65	73.44	90.11
Fme-3	0	70.15	77.61	88.47
Fme-4	0	71.60	76.14	87.34

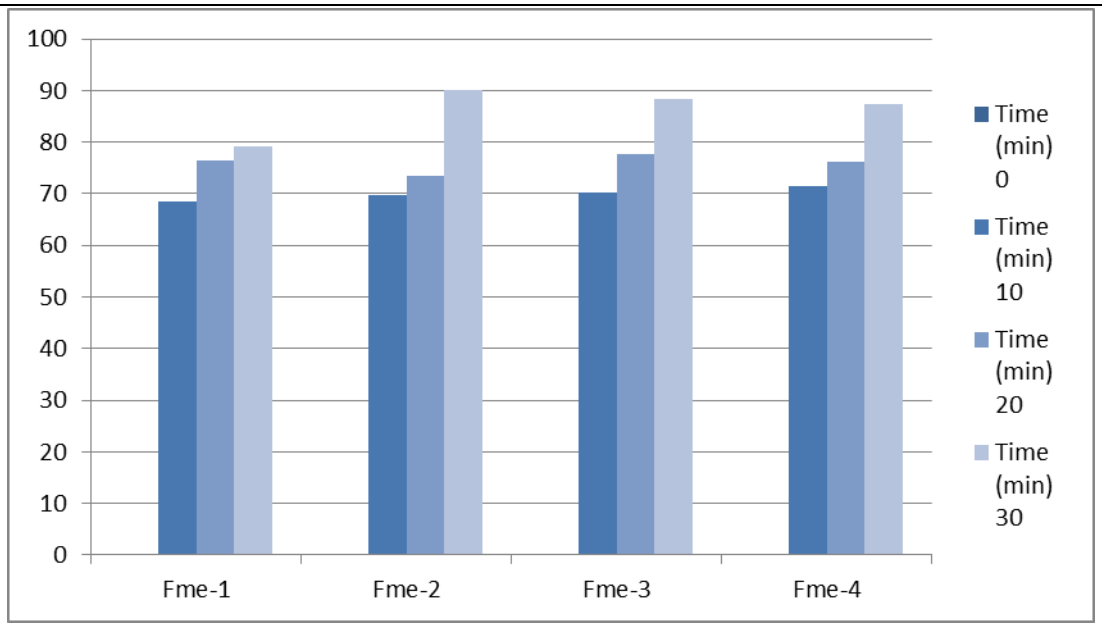

Figure 7 Dissolution data of optimized batches

Table 12 Evaluation parameters of a batch that was kept for stability study:

Evaluation Parameters	Hardness (%)	Friability (%)
Before stability Storage	5.9	0.25
After 1 month Storage	5.8	0.5
After 2 month storage	6.1	0.35
After 3 month storage	6.0	0.4

The formulations were periodically removed from storage afterward and subjected to physical parameter analysis; the results are shown in the table above. The examined parameters before and after the formulations had been aged in storage did not significantly differ from one another; all were found to be within acceptable bounds.

CONCLUSION

Expanded discharge frameworks were made a long time back to resolve these issues. The expressions "broadened discharge," "expanded activity," "delayed discharge," "controlled discharge," "broadened activity," "planned discharge," "warehouse," and "redepository measurement structures" allude to sedate conveyance frameworks that expected to accomplish a drawn out remedial impact by ceaselessly delivering prescription over a lengthy timeframe following the organization of a solitary portion. The test of making new drugs has expanded the emphasis on making novel medication conveyance frameworks for both new compound substances and existing medications. The range of formulations' mean particle sizes (effective diameters) was 46.90.358 nm to 1043.3510.2 nm. The powder was too solid to pass through the funnel, although Etodolac's granules had an angle of repose that ranged from 21.99° to 23.70°. Carr created a method to measure the ability of the powder to flow from bulk densities called % compressibility. Etodolac's % compressibility was discovered to be 54.05. A friabilator was filled with a pre-weighed sample of tablets, and it was rotated 100 times. The range of hardness was 4.9% to 5.7%. Friability was between 0.1 and 0.5. The examined parameters before and after the formulations had been aged in storage did not significantly differ from one another; all were found to be within acceptable bounds. The consequences of writing research that has been progressing have been expounded on a few creation and application innovations for expanded discharge tablets.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest.

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