e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:05/Issue:01/January-2023 Impact Factor- 6.752 www.irjmets.com

FORMULATION DESIGN AND COMPARATIVE EVALUATION OF EXTENDED-RELEASE TABLET

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ABSTRACT

Tablets are a type of dosage form used for pharmaceuticals. It consists of an excipient powder mix and the active ingredient compressed or compacted into a fixed dose. Effective tableting aids may include diluents, binders or granulating agents, glidants (fluid aids), and glidants. Acceleration of tablet disintegration in the gastrointestinal tract. Flavorings or sweeteners to improve the taste. Pharmaceutical formulation goals to be achieved during work include tablets with long release times and strong physical strength. A tablet contains the highest concentration of medicinal ingredients while maintaining a constant unit of content per tablet. Multiple daily doses of the drug are required to keep the drug concentration within the therapeutic range. Increase patient compliance and avoid excessive dosing intervals. Development of a stable and safe oral formulation containing a time-release anti-inflammatory drug that can control arthritis. To determine the optimal dissolution profile for the dosage form being developed. Formulations were determined by comparing the in vitro dissolution profile to that of the innovative product. The aim of this study was to develop a pharmaceutically similar, stable, cost-effective, and improved-quality extended-release tablet formulation of etodolac. Polymers such as HPMC, ethylcellulose, Carbopol 934, MCC, and magnesium stearate are used to formulate tablets and conduct in vitro drug release studies.

Keywords: Extended-Release Tablet, Etodolac, Polymers, In-Vitro Study.

I. INTRODUCTION

A tablet is a dosage form used in pharmaceuticals. It is made up of a powdered mixture of active ingredients and excipients that is pressed or compressed into a solid dosage. To facilitate efficient tableting, excipients can include diluents, binders or granulating agents, glidants (flow aids), and lubricants: disintegrate to encourage tablet break-up in the digestive tract; sweeteners or flavours to improve taste; and pigments to make the tablets visually appealing [1].

A polymer coating is frequently used to make tablets smoother and easier to swallow, to manage the active ingredient's release rate, to make them more resistant to the environment (increasing their shelf life), or to improve their look. Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Early modified release products were often intramuscular/ subcutaneous injections of suspensions of insoluble drug complexes, e.g., procaine penicillin, protamine zinc insulin, insulin zinc suspensions or injections of the drug in oil, e.g., fluphenazine decanoate [2].

Advances in technology have resulted in novel oral modified- release dosage forms. Many terms are used to describe modified-release products including extended-release, prolonged-release, controlled-release, controlled-delivery, slow release and sustained-release. Delayed-release Products are modified-release, but they are not extended-release by definition. They entail the release of a discrete amount(s) of medicament after it has been administered. e.g., Enteric-coated products, have a lag time in which little or no absorption takes place [3].

While there are a variety of modified-release pharmaceuticals available as prescription and over-the- counter medications, only a small number have been proved to provide a therapeutic benefit. Rather for being designed for clinical benefit, several of the formulations appear to have been devised to extend patents or give a marketing advantage over conventional-release medications. Various prototype formulation trails were taken and assessed with various quality controls such as dissolving and assay to achieve these goals [4].

By comparing the in vitro dissolution profile to that of the innovator product, the recipe was determined. The goal of this study was to create a pharmaceutically similar, stable, cost-effective, and quality-improved Etodolac extended-release tablet formulation. To formulate a tablet employing polymers such as HPMC, Ethyl cellulose,

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Carbopol 934, MCC, Magnesium Stearate, and others and to conduct an in vitro release research on the drug [5, 6].

II. MATERIALS & METHODS

Table no 01- Materials used in the formulation of etodolac extended release tablet [7-10]

Ingredient Names	Functional / category
Etodolac	API
Talc	Lubricant, anticaking agent
Hydroxy propyl methyl cellulose	Release controlling polymer
Carbopol 934	Polymer
Microcrystalline cellulose	Texturizer, anticaking agent
Mannitol	Diluent/ Bulking Agent
Magnesium stearate	Lubricant

Table No 02- Formulation Table of tablet

Ingredient for tablet	Formulation Batches				
	F1	F2	F3	F4	F5
Etodolac (mg)	400	400	400	400	400
HPMC (%)	1	2	---	---	1
Carbapol 934 (%)	---	---	1	2	1
Talc (mg)	5	5	5	5	5
Magnesium Stearate (mg)	7	7	7	7	7
MCC (mg)	86	82	86	82	82
Mannitol (mg)	QS to 500 Mg				

Methods

HPMC as a synthetic polymer, Carbopol 934 as a stabilizer and also water-soluble polymer, microcrystalline cellulose, Magnesium stearate, and Tale were used to make Etodolac prolong release tablets utilizing the Direct Compression technique. Except for magnesium stearate and tale, etodolac and other similar excipients are weighed properly. Prior to combining, all materials are mixed properly. After that, place all of the ingredients in a glass mortar and triturate until uniformly combined. Then talc and magnesium stearate were added to the mix. A tablet compression machine was used to compress the powder combination into a tablet with punches on a tablet machine and make tablet [11].

The release rate regulating polymer hydroxy propyl methylcellulose was used in varied ratios to manufacture etodolac matrix tablets using the direct compression method. Bulk density, tapped density, Car's index, Hauser's ratio, and angle of repose were all used to analyses the granules' flow qualities. FTIR, diameter, weight variation test, hardness, friability, disintegration test, in vitro drug release, release kinetics, and stability studies were used to access the tablet for drug polymer compatibility [12].

III. MODELING & ANALYSIS PREFORMULATION STUDY

Solubility

A qualitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing a fixed quantity of solute or vice versa affects each addition the system is vigorously shaken and observed visually. Etodolac & Solvent. Take a Dilution 1mg drug with 1 ml of particular solvent that is Primary Solution. Second one 1ml sample from Primary Solution with 10 ml dissolution medium (0.1 N HCl) that is observe solution after preparing solution. Record Absorbance of observe solution by UV Spectroscopy with a particular wavelength & Plot the graph & formed the bar graph of all observation [13].

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Melting Point-

Collect the one side-sealed capillary, Thiele tube, Liquid paraffin, Thread, burette stand, and Thermometer from the laboratory. Fill the API in the capillary & bind that to the thermometer for temperature reading. Deep that bind capillary & thermometer in thiele tube. Provide that heat to the tube with help of a gas burner & observed the melting point & note-down the reading [14].

UV Analysis of Drug (API) Sample

For Acidic Gastric Media –

Preparation of 0.1N HCL solution (Solvent) which is act as a gastric fluid. Preparation of 1000 PPM Solution (Stock Solution) for that 100mg drug (Well-dissolved small amt soluble solvent) with 100ml solvent. Preparation of 10 PPM Solution [1ml sample from 1000-ppm solution + 100 ml Stock solution]. Preparation of 1,2,4,6,8,10 PPM Solution [1ml sample form 10ppm solution + 10ml Solvent = 1ppm sample]. Observed the absorbance by UV Spectroscopy with specific wavelength & plot the graph [15]

For The Basic Gastric Media-

Preparation of stock solution (7.4 Phosphate buffer) Weigh 8 gm of sodium chloride then add it to the sufficient amount of distilled water. After that weigh 1.44 gm disodium hydrogen phosphate and 0.24 gm potassium dihydrogen phosphate. Add it into the prepared sodium chloride solution then weigh 0.2 gm potassium chloride. Then dissolved all the weighed samples in a sufficient amount of distilled water. Finally, maintain the solution up to 1000 ml with distilled water and, adjust the pH, if necessary. Follow the other procedure for dilution as per the acidic media procedure. Observed the absorbance by UV Spectroscopy with a specific wavelength & plot the graph [16]

Evaluation Study –

Precompression study-

The angle of Repose (Ø)

The frictional force in a loose powder or granules can be measured by the angle of repose. The angle of repose is defined as the maximum angle possible between thesurface of a pile of the powder and horizontal plane [17]

Tan Ø= H/r

Were,

Ø= angle of reposeis the height of the cone, R= radius of the base of the cone

Different ranges of flow ability in terms of angle of repose are given in the below table.

Table No 03- The Specification of Angle of Repose

The angle of Repose (ɵ)	Flow
>25	Excellent
25-30	Good
30-40	Passable
<40	Very poor

Method-

A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. The cone formed on a graph sheet was taken to measure the area of the cone, thereby evaluating the flow ability of the granules. The height of the pile was also measured.

Bulk Density & Tap Density -

Loose bulk density (LBD) and tapped bulk density (TBD) of dose form and the dosage form blends were determined using bulk density apparatus. The pure drug was passed through the #18 sieve to break the clumps if any. Accurately weighed 5 g of the drug or 25 g of polymers was placed in a 100 ml graduated measuring cylinder. The initial volume was observed. The cylinder was tapped initially 100 times from a distance of 14 ± 2 mm. The tapped volume was measured to the nearest graduated unit. The tapping was repeated additional 100 times. Again, the tapped volume was measured to the nearest graduated unit. The same thing was done for

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powder blends of the dosage form. The LBD and TBD were calculated in g per ml using the following [18, 19].

Bulk Density = weight of the powder/volume of the packing

Tab Density = weight of the powder / tapped volume of the packing

Hausner ratio-

The Hausner ratio of the powder was determined by the following equation.

Hausner ratio = TBD / LBD

The lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Post-compression parameters study-

Weight Variation & Content Uniformity-

The weight variation statistical quality control test is used to confirm uniformity of the dosage unit and therefore also to support product safety, identity and quality. In the production of food and beverages, checking the weight of packages provides fast confirmation that fills quantities meet legal requirements [20].

Table no 04 - Table contains the Specific limit of weight variation as per various regulatory

IP/BP	USP	Limit
More than 80mg or less than 250mg	130mg to 324mg	± 7.5%
250mg or more	More than 324mg	± 5%

Thickness-

Thickness of tablets indicates the strength to withstand compression force applied during manufacturing process. Thickness of tablets was measured by digital caliper [21].

Hardness-

Test Hardness (diametric crushing strength) is the force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablets should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufacturers and with the different types of tablets. The hardness was tested using Monsanto tester. “Hardness factor”, the average of the six determinations, was determined and reported. The force was measured in kilograms per centimeter square [22].

Friability-

Test Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Permitted friability limit is 1.0 %. Roche friabilator (Electrolab, Mumbai) was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friability. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friability and intact tablets were again weighed collectively [23]

% Friability = W1 – W2 /W1 × 100

Where, W1 is weight of the tablet before the test & W2 is weight of the tablet after test.

Disintegration study-

Complete decomposition is defined as a state where no residue, except for fragments of the tablet shell or undissolved tablet shell, remains on the display of the test apparatus or adheres to the bottom surface of the dish if the disc is used; if there is still another residue then it is soft mass without a core material. The mean disintegration time of tablets containing microcrystalline cellulose or dicalcium phosphate dihydrate was 37 min and 44 min, respectively. Tablets containing corn starch or sodium carboxy-methylcellulose break down very slowly and adhere firmly to the gastric mucosa. In the project, we have to do the disintegration test in two different gastric media i.e., acidic & basic media [24].

Procedure-

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Prepare 1000 ml of both gastric fluids. For Acidic (0.1N HCl Solution) [8.5 ml of Concentrated HCL+ 1000 ml distilled water]. For Basic (7.4 pH Buffer solution) 8 gm sodium chloride + 1.44 gm disodium hydrogen phosphate + 0.24 gm potassium dihydrogen phosphate + 0.2 gm of potassium chloride + Distilled water (100 ml). Place both solutions in the disintegration flask, allow maintaining temperature (Body temp). Place the Tabletin the test tube in the disintegration apparatus then start the instrument & observed the disintegration time [25, 26].

Drug content-

The five Tablets were weighed and empty to obtain powder equivalent to 150 mg of Etodolac**.** Dissolved in a suitable quantity of buffer, the solution was filtered and suitably diluted**.** Drug content was recorded by a using UV spectrophotometer at a specific wavelength [27]

In vitro study-

Dissolution studies-

In Vitro dissolution studies for all the prepared tablets and the marketed available tablets were carried out using the USP paddle method at 50 rpm in 900 ml of buffer solution 0.1N HCL as dissolution media, maintained at 37 + 0.5°. 5 ml of sample was withdrawn from the dissolution medium at the specified regular intervals, filtered through Whatman filter paper, and assayed spectrophotometric at 280nm. An equal volume of pre-warmed (37° C) fresh medium was replaced with the dissolution medium after each sampling, to maintain the constant volume throughout the test. Then the cumulative percentage of drug release was calculated and represented graphically [28-30]

Tablet No 05- Table Contain the Specification of Dissolution Study

Apparatus	**USP Apparatus II (Paddle)**
Medium	0.1N HCL
Speed	50 RPM
Temperature	37°C ± 0.5°C
Medium volume	900mL
Time points	Every 30 min up to 6 Hr

IV. RESULT & DISCUSSION

Solubility

Table No 06- The Table contains the Solubility of API with absorbance

Solvent	**Absorbance**
Ethyl acetate	0.055
Chloroform	0.049
Methanol	**0.099**
Dimethyl Sulphoxide	0.065
Methyl Chloride	0.059
Ethanol	0.042
Water	0.0015

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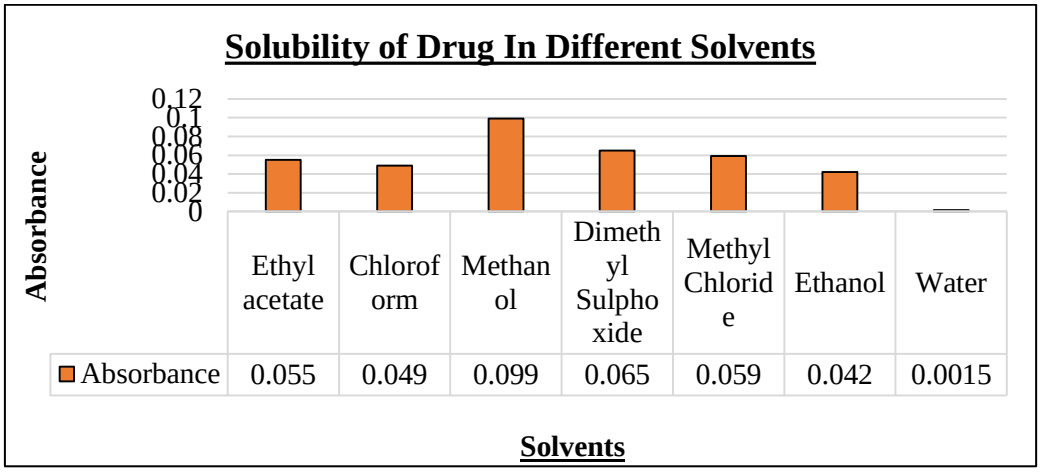


Graph Number 01- Solubility Graph of drug API -Etodolac.

As per the characterization study of solubility API (Drug) has the highest absorbance in **methanol solvent**, according to the solubility studies, thus we choose methanol as our organic solvent for formulations.

Melting Point-

Table No 07- The table contains the observation of the melting point.

API Sample	Reference MP □	Observed MP□	Final MP □
Etodolac	145-148	145	145
		145	
		147	

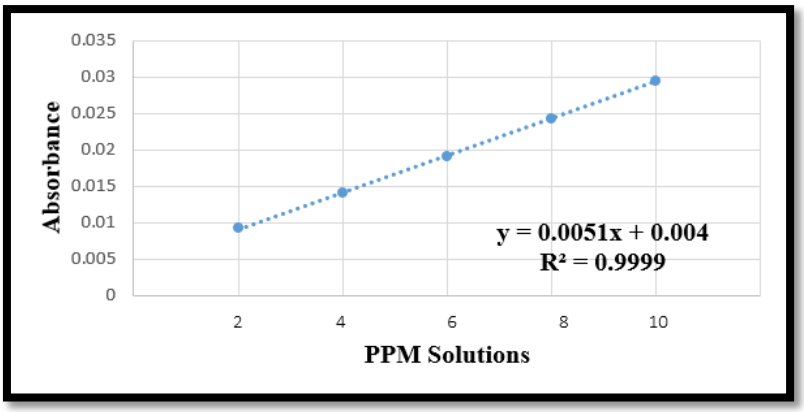
The melting point of **etodolac** is **145** □ observed.

UV Analysis of Drug (API) Sample-

For Acidic Gastric Media-

Table No 08- The Table contains the absorbance of particular samples for acidic media.

PPM Solution	Absorbance
2 ppm	0.0092
4 ppm	0.0141
6 ppm	0.0191
8 ppm	0.0242
10 ppm	0.0294



Graph Number 02- The Graph Contains Etodolac UV Analysis for Acidic Media.

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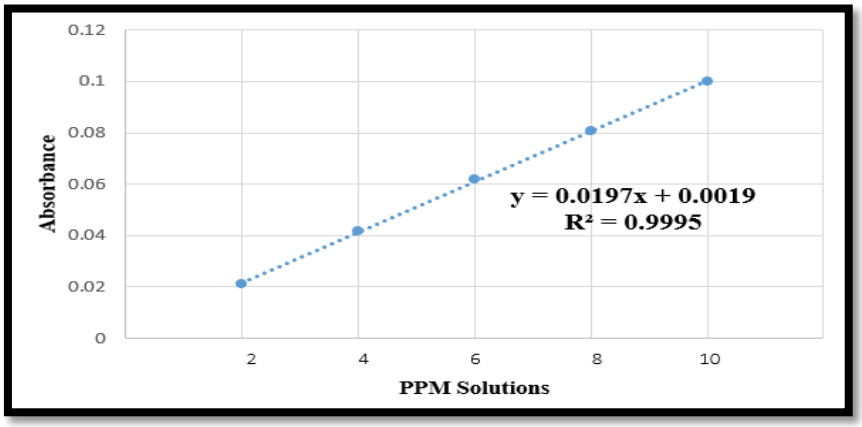
For Basic Gastric Media-

Table No 09- The Table contains the absorbance of particular samples for basic media.

PPM Solution	Etodolac
2 ppm	0.0209
4 ppm	0.0416
6 ppm	0.0619
8 ppm	0.0809
10 ppm	0.0998



Graph Number 03- The Graph Contains Etodolac UV Analysis for Basic Media.

The Maximum wavelength (λ max) of API (Drug) by spectra analysis is (Etodolac) 298 nm.

The regression value of API (Drug) is as follows for different Media-

1] The regression value of the Drug of Etodolac (Acidic) is **R^2=0.9999**

2] The regression value of Drug of Etodolac (Basic) is **R^2=0.9995**

Pre-compression parameters study-

Table no 10– The all Pre compression parameter study in the table

Formulation Number	Angle of repose Degree (º)	Bulk Density (mg/ml)	Tap Density (mg/ml)
F1	27.90	0.290	0.825
F2	25.70	0.5860	0.7760
F3	25.60	0.5770	0.7983
F4	31.50	0.5800	0.8730
F5	28.30	0.5910	0.7894

According to the observation of mention Pre- Tablet filling parameter study conclude that the all formulations has passes the all test for filling of tablets. The All formulation having good flow ability, filling capacity & packing capacity.

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Post – Compression Parameters Study-

Weight Variation-

Table No 11 - The weight variation of various formulation

Sr. no	Tablet	Weight of Tablet (mg)				
		F1	F2	F3	F4	F5
1	T1	500	500	500	500	500
2	T2	499	502	500	502	498
3	T3	500	500	500	500	500
4	T4	499	502	500	502	502
5	T5	500	500	500	500	500
6	T6	500	500	500	500	500
7	T7	500	500	500	500	500
8	T8	500	503	502	500	502
9	T9	500	500	500	500	500
10	T10	500	500	500	500	502
11	T11	502	500	500	500	500
12	T12	500	500	498	500	500
13	T13	500	500	500	500	500
14	T14	502	500	498	502	498
15	T15	500	500	500	500	500
16	T16	500	500	500	500	498
17	T17	500	500	500	500	500
18	T18	502	500	500	500	502
19	T19	500	500	500	500	500
20	T20	499	500	500	500	498
Total weight		10003	10007	9998	10006	10000
Averages weight		500.15	500.35	499.9	500.3	500
Upper limit		502	503	502	502	502
Lower Limit		499	499	498	500	498
% Variation		0.59982	0.79944	0.80016	0.39976	0.8

By find out average weight, Total weight, Upper & lower limit of Tablet the determination of weight variation of all batches has been done in that as per specification the **% weight variation** is acceptable. As per that view the all Formations is pass this test but from all formulations the formulation number **F4** have very low variation & Formulation number **F3** having high variation.

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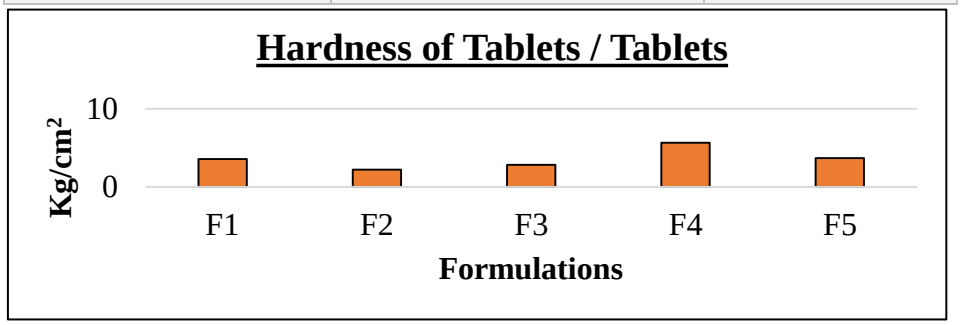
Hardness-

Table No 12 - The table contains the formulations hardness.

Formulation number	Testing (Kg/cm²)	Mean (Kg/cm²)
F1	3.56	3.56
	3.56	
	3.56	
F2	2.15	2.22
	2.36	
	2.15	
F3	2.36	2.82
	2.59	
	3.52	
F4	5.66	5.66
	2.33	
	5.66	
F5	3.66	3.66
	3.33	
	3.66	

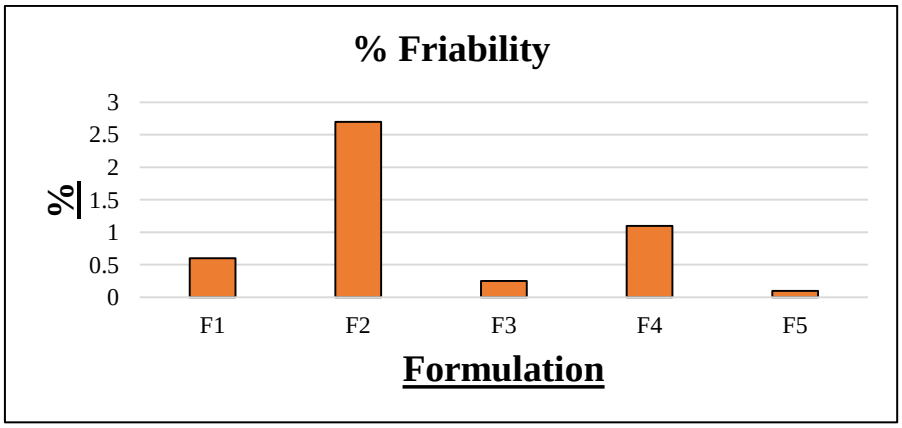


Graph Number 04 - The graph contains the formulations hardness

The tablet's hardness should be less than 4 Kg/cm³ in order to comply with USP standards. The formulation with the very least hardness, F2, and the formulation with the most hardness, F4, are both available.

Friability Test-

Table Number - The table contains the Friability of different formulation



Graph Number 05- The graph contains the Friability of different formulation

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The friability of the tablet should be less than 1% in accordance with USP requirements. F5 is the formulation with the very lowest friability, and F2 is the formulation with the highest friability.

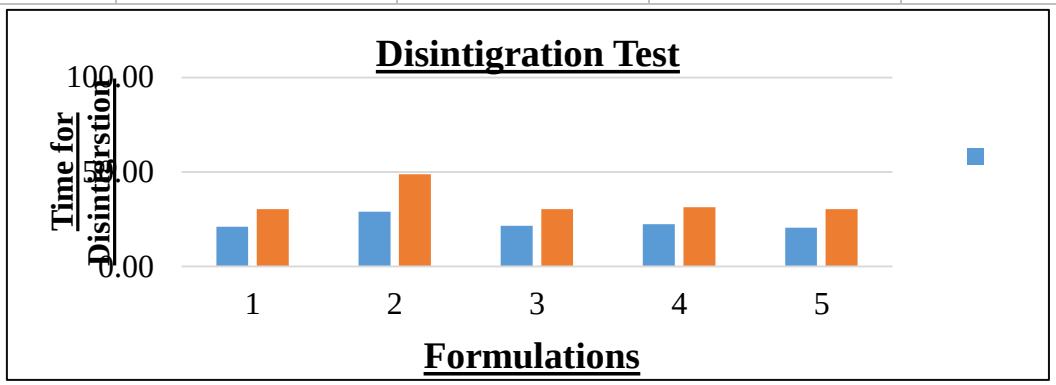
Disintegration Test-

Table No 13 – The Disintegration time of various formulations in Acidic Gastric Media-Stomach

Formulations	Time of Disintegration of Tablet (min) for Acidic Gastric Media-Stomach			
	C1	C2	C3	Mean
F1	21.18	21.56	20.2	20.98
F2	29.03	29.44	28.59	29.02
F3	22.56	21.55	20.59	21.57
F4	22.26	22.56	22.48	22.43
F5	20.56	20.56	20.46	20.53

Table No 14- The Disintegration time of various formulations in Basic Gastric Media- Intestine

Formulations	Time of Disintegration of Tablet (min) for Basic Gastric Media- Intestine			
	C1	C2	C3	Mean
F1	30.49	30.18	30.54	30.40
F2	48.42	49.2	48.59	48.74
F3	30.12	30.52	30.49	30.38
F4	30.4	31.56	32.12	31.36
F5	30.12	30.52	30.49	30.38



Graph number 06- The graphical representation of disintegration time of formulation in two different media

The Determination of disintegration time take place as per standard method & instrument take place in that due to the extended release Tablet the method follow by two different medium have to done i.e., Acidic media & basic media form the Stomach & intestine respectively as per observation the Tablet disintegrate in acidic media in short duration & basic media in long duration

Drug Content-

Table No 15- The Drug content in formulation in percentage

Formulations	Drug Content (%)
F1	94.83
F2	93.64
F3	95.45
F4	94.56
F5	98.63

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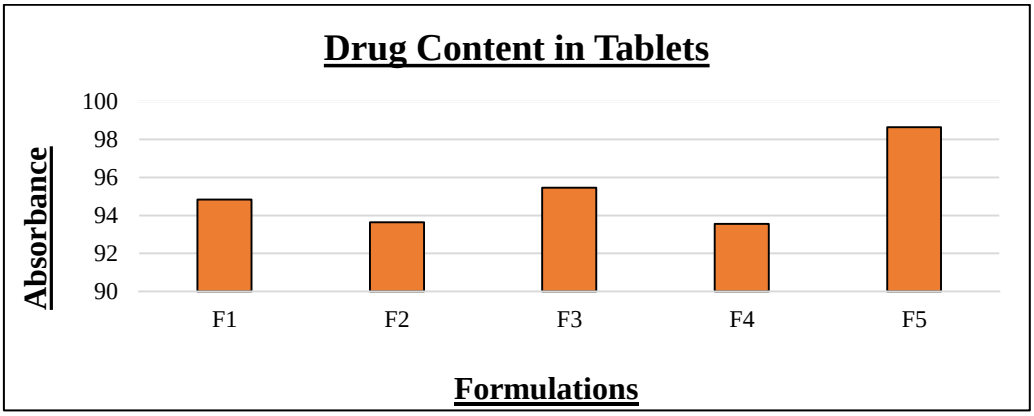


Graph number 07- The Percentage Drug content in formulation

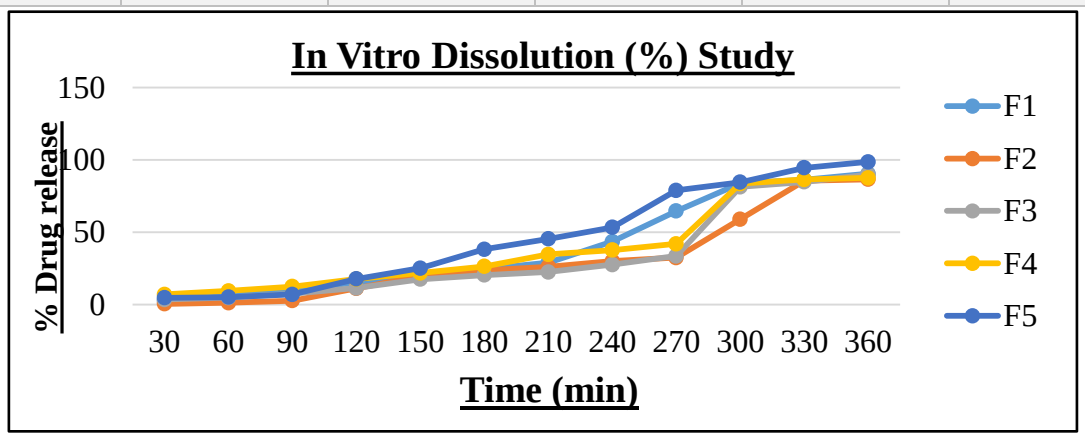
By follow standard operating procedure of drug content find out of that has been done form that all concludes that Formulation number F5 having highest drug content & Formulation number F2 having very low.

In Vitro Dissolutions study-

In vitro Dissolution Study-

Table no 16 - In vitro dissolution for various time intervals

Time (Min)	In Vitro Dissolution (%) Study				
	F1	F2	F3	F4	F5
30	2.485	0.3733	3.459	6.982	4.651
60	6.098	1.2326	4.7465	9.348	5.0684
90	11.265	2.6153	7.359	12.349	6.991
120	15.065	11.141	11.427	17.578	17.691
150	19.436	19.623	17.527	21.792	25.066
180	24.456	23.685	20.397	26.289	38.177
210	28.978	26.102	22.456	34.609	45.341
240	43.438	29.954	27.498	37.628	53.315
270	64.593	32.437	33.568	41.893	78.897
300	83.764	58.967	81.367	83.623	84.612
330	86.38	85.546	84.735	86.478	94.554
360	90.42	86.536	89.82	87.56	98.62



Graph Number 08– The graph contains the percentage of drug release of all the formulations against specific time intervals.

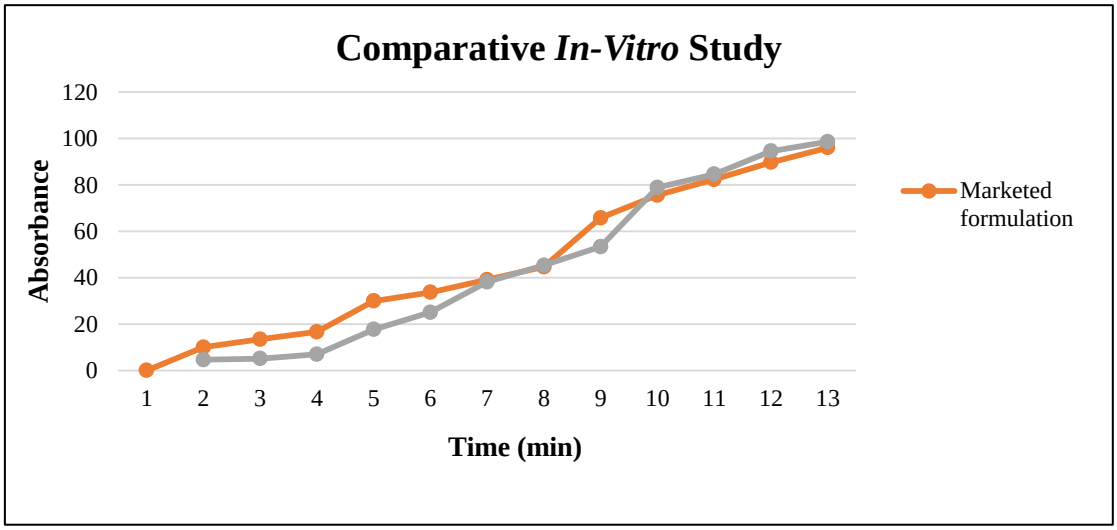
e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:05/Issue:01/January-2023 Impact Factor- 6.752 www.irjmets.com

According to graph & the Observation table we see that the all formulation of solid dispersion tablet having adequate drug release capacity but as compare to each other the formulation number, F2 (86.53%) having very low percentage Drug release whereas the formulation number F5 (96.62%), having High percentage drug release.

Comparative Study-

Table No 17 - The Comparative In-Vitro Study of Marketed & Optimizes Formulation (% Drug Release)

Time (Min)	Marketed formulation Drug Release (%)	Optimizes Formulation Drug Release (%)
30	10.028	4.651
60	13.448	5.0684
90	16.612	6.991
120	29.951	17.691
150	33.662	25.066
180	39.095	38.177
210	44.628	45.341
240	65.773	53.315
270	75.525	78.897
300	82.329	84.612
330	89.671	94.554
360	96.029	98.62



Graph number 09 - The Comparative In-Vitro Study of Marketed & Optimizes Formulation

V. CONCLUSION

The in-vitro comparative study of marketed formulation & Optimize Batch (Dissolution Study/ Drug release Study) has been performed for 6 hr. by USP II apparatus i.e., Paddle type of apparatus used in that at normal body temperature this test has been performed. At the end of study resulted that the optimized Formulation having constantly increase & highest **(98.62 %)** drug release capacity & traditional marked formulation number having drug release capacity **(96.029 %).** Hence according to graph analysis we can say that the optimized formulation as good as marked formulation.

VI. CONFLICTS OF INTEREST

There are no conflicts of interest or disclosures regarding the manuscript.

ACKNOWLEDGEMENT

The authors express their sincere gratitude to Pravara Rural College of Pharmacy, Pravaranagar (Loni Bk), University Libraries, and all other sources for their cooperation and advice in writing this review.

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