Formulation And Evaluation of Microspheres by Using Spray Drying Technique

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Abstract—**One NSAID is ketoprofen. medications that don't cause inflammation. medication is a member of the NSAID class. Since it is a BCS class II medication, The work plan has been broken up into various sections. first gathering theoretical data through a review of the literature and a pharmacological profile. The acquisition of materials and their standardization came next. Preformulation experiments were conducted to determine the medication's color, taste, odor, and melting point. The results showed that these characteristics were equal to those specified in the analytical profile of the drug material. There was no interaction between the medicine and carrier, according to the compatibility analysis conducted using FT-IR spectroscopy and an FT-IR spectrophotometer. utilizing ethyl cellulose, Eudragit RS, Eudragit RL, and Eudragit E100 as retreading polymers, the ketoprofen microspheres were created utilizing the spray drying process. A variety of metrics, including practical yield, micromeritic analysis, particle size measurement, drug content, invitro drug release, scanning electron microscopy (SEM), and stability investigations, were assessed for the produced formulations. The Micromeritic investigation revealed that SD had superior flow characteristics. Additionally, it was discovered that the methods used in this study to create spray dried microspheres might result in a formulation with a consistent drug content. Given the medicine Ketoprofen's solubility nature, a dissolution research is crucial. We can learn more about how the medicine will behave within the body by using in vitro sink settings with the appropriate dissolving medium.**

The amount of medication solubilized and the rate of dissolution are two factors that are examined in conjunction with the dissolution investigations. An increase in carrier concentration accelerates the rate of dissolution, according to the in-vitro investigation. A higher rate of disintegration was noted in the order of A good solubility profile depends on the medication remaining in its amorphous form in the formulation, which is ensured by stability tests. After two months of stability testing at 40ºC and 75% relative humidity, the chosen optimized formulation was assessed for drug content and dissolution. Physical appearance, drug content, and invitro drug release did not significantly change, according to alter analysis results.

I. INTRODUCTION

Maintaining therapeutic blood or tissue levels of the medication for a long and predetermined amount of time is the aim of a sustained release dosage form. Usually, this is achieved by trying to get "zero-order" release from the dose form. medication release from the dosage form that is unaffected by the quantity of medication in the delivery system is known as zero-order release (i.e. a constant release rate). This kind of release is typically not achieved by sustained-release systems, which instead attempt to simulate zero-order release by administering the drug in a gradual first-order manner (i.e., concentration release dependent). It is also possible to think of systems classified as prolonged release as attempts to achieve sustained-release delivery.[1]

Many oral extended-release rate dosage forms, such as sustained release (SR), sustained action, prolonged action, protracted action, and retarded release, have been referred to as "controlled-release drug products." Drug companies introduced these terms for extended release (ER) dosage forms as a marketing phrase or to indicate a unique design for creating an ER dosage form. [1]

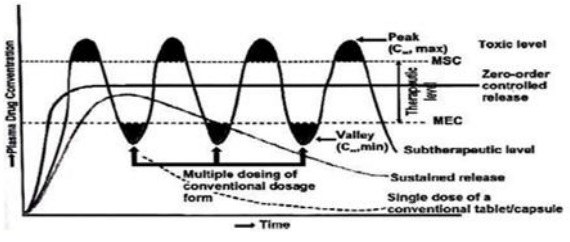


Figure 1: A hypothetical plasma concentration vs time profile from conventional. multiple and single doses of sustained release drug delivery formulations.

Advantages
- Less frequent dosing • Consistent blood medication levels with minimal variation
- Enhanced ease and patient compliance • Steers clear of nighttime dosage
- A consistent therapeutic outcome
- Better bioavailability (for some medications)
- Reduced medical expenses

Disadvantages
• A potential decrease in systemic availability
• A poor connection between in vitro and in vivo
• Dose dumping risk • Drug retrieval in toxicity is difficult.

A. Properties of Physicochemical
• The dosage
• Solubility in water and pKa
• Stability of drugs the size and diffusivity of molecules • Binding of proteins
B. Characteristics of Biology
• Rate of absorption
• The distribution
• The metabolism
• Removal and half-life

The best SR medications:
The solubility is moderate.
• Half-life: 2–8 hours
• A broad therapeutic index Stability in the gastrointestinal tract is good. SR/CR Drug Release Principles Principal mechanisms 1. Systems with diffusion control 2. Systems with dissolution control 3. Systems of diffusion plus dissolution 4. Systems of osmosis

Microspheres
Definition Microspheres are spherical particles (1–1000 μm) made of biodegradable or synthetic polymers, where the drug is dispersed within a polymer matrix. Common Polymers
- Natural: Albumin, Gelatin, Chitosan, Starch, Sodium alginate
- Synthetic: Polylactic acid (PLA), Polyglycolic acid (PGA), Cyanoacrylates

Advantages of Microspheres
• Controlled & targeted drug delivery
• Improved bioavailability
• Reduced drug toxicity
• Protection from moisture, oxygen, light
• Taste masking • Reduced gastric irritation
• Enhanced stability
•Improved handling of liquids/toxic substances

Applications
• Prolonged release dosage forms
• Enteric-coated delivery
• Taste masking
• Protection from environmental degradation
• Intrauterine devices
• Improved tablet flow properties

Ideal Properties of Microsphere Carriers
• Biocompatible & biodegradable
• Controlled drug release
• Stable & sterilizable
• Reduce toxicity
• Enhance therapeutic efficacy

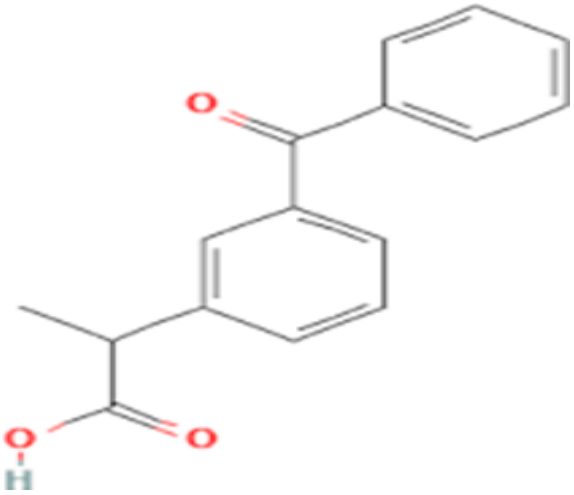
Preparation Methods of Microspheres Major techniques include:
1. Protein gelation technique
2. Single emulsion method
3. Double emulsion method
4. Multiple emulsion method
5. Solvent evaporation
6. Sonication
7. Spray drying
8. Spray congealing
9. Phase separation (coacervation)
10. Polymerization techniques
11. Solvent extraction

Spray Drying Technique
Principle Liquid feed is atomized into droplets → contacted with hot air → solvent evaporates → dry microspheres collected. Key Steps

1. Concentration
2. Atomization
3. Droplet-air contact
4. Drying (two stages)
5. Separation Types of Spray Dryers
• Two-stage dryer
• Horizontal dryer
• Vertical dryer
• Fluidized spray dryer Advantages

• Rapid drying
• Suitable for heat-sensitive materials
• Controlled particle size
• Continuous production

Ketoprofane



IUPAC-Name (RS)-2-(3-benzoylphenyl) propanoic acid.

II MATERIALS AND METHODS

Preformulation Studies of Ketoprofen

• Organoleptic properties Ketoprofen was tested for organoleptic properties such as appearance, colour, odor, taste etc.

• Appearance: Transferred approximately 2gm of the sample on a white paper spreaded uniformly and examined visually.

• Colour: A small quantity of pure ketoprofen powder was taken in a butter paper and viewed in well illuminated place. Ketoprofen is a white or off-white, non-hygroscopic, fine to granular powder, with the melting point about 95° C. Taste and odor: ketoprofen was tested manually for its taste and odor. Odorless.

• Melting point determination Melting point of the drug was determined by capillary method using Melting point apparatus. Here, the capillary tube was filled by pressing the open end gently into sample by tapping the bottom of the capillary on a hard surface so that the drug pack down into the bottom of the tube. When the drug packed into the bottom of the tube, the tube was placed into the slot behind the eyepiece on the Melttemperature. Make sure the unit is plugged in and set to zero, and then turn it on. The temperature was noted when the drug start to melt and the drug till complete melt [51]

• Solubility studies the spontaneous interaction of two or more substances to form a homogenous molecular dispersion is called solubility. For quantitative solubility study, excess amount of drug was taken in thoroughly cleaned test tubes containing 3 ml of different solvents (Methanol, Ethanol, Acetone, Chloroform, 0.1N HCl, water, STF pH 7.4) and test tubes were tightly closed. These test tubes were shaked on water bath shaker for 24 h at room temperature. After 24 h each sample was centrifuged 15,000 rpm and supernatant was withdrawal. After that supernatant was filtered and filtrates was suitably diluted and determined spectrophoto metrically at 260 wavelengths.[51]

• Compatibility study the compatibility study was done by FTIR spectroscopy by using FTIR spectrophotometer (thermo Nicolet) [13. FT-IR spectra were obtained by an FT-IR spectrophotometer using the potassium bromide (KBr) disk method by means of a hydrostatic press. The procedure consisted of dispersing a sample (druf and drugcarrier mixture) in KBr and compressing into disk by applying a pressure by hydraulic press. Data were collected over a spectral region from 4000 to 400cm-1 with a resolution of 2 cm-1. The interaction between drug and excipients was observed IR- spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug. And obtained data spectra

• Spectroscopic studies of Ketroprofen

• Standard calibration curve of Krtoprofen in Phosphate buffer (pH 7.4)- Method Calibration curve of Ketoprofen was prepared in phosphate buffer (pH 7.4) at different Dilutions.

•Preparation of stock solution Ketoprofen (10 mg) was accurately weighed and dissolved in phosphate buffer (pH 7.4). The final volume was made up to 100 ml with phosphate buffer (pH 7.4) to obtain a concentration of 100 ug/ml. This stock solution was used to prepare further standard
solutions of drug.

• Preparation of standard solution

Aliquots (0.55.0 ml) of stock solutions of Ketoprofenwere transferred into series of 10 ml volumetric flask and volume was made up to the mark with phosphate buffer (pH 7.4) to give the concentration range from 5 to 50 ug/ml. The

absorbance was measured at 260 nm against the reagent blank. From the absorbance, standard curve was plotted. [14]

Preparation of spraydried Microspheres of ketoprofen1.Measured quantities of Drug Ketoprofen and Ethyl Cellulose polymer (As per table showed), were dissolved in methanol. The resultant dispersion was constantly stirred on magnetic stirrer while being subjected to spray drying process. Spray drying was carried out using a spray dryer in a cocurrent mode. Under different set of conditions.

2.Measured quantities of Drug Ketoprofen and Eudragit E100 polymer (As per table showed), were dissolved in methanol. The resultant dispersion was constantly stirred on magnetic stirrer while being subjected to spray drying process. Spray drying was carried out using a spray dryer in a cocurrent mode. Under different set of conditions.

3.Measured quantities of Drug Ketoprofen And Eudragit RS Eugradit Rl polymer combination of polymer. (As per table showed), were dissolved in methanol. The resultant dispersion was constantly stirred on magnetic stirrer while being subjected to spray drying process. Spray drying was carried out using a spray dryer in a cocurrent mode. Under different set of conditions indicated in table 04.

Sr. No.	Process parameters	Values
1	Inlet temperature	90 ˚C
2	Outlet temperature	70 ˚C
3	Feed flow rate	2 ml/min
4	Pressure	100Kpa
5	Automization pressure	1

Table 4: Spray drying process parameters

III. RESULTS AND DISCUSSION

Preformulation study of Ketoprofen

Sr. No.	Physical characters	Specifications/Limits	Observations
1	Nature	fine to granular powder.	fine to granular powder.
2	Colour	white or off-white	white or off-white
3	Odor	Odorless	Odorless
4	Taste	unpleasant taste	unpleasant taste

Table 6: Physical characters of the Ketoprofen drug

The physical characters of Ketoprofen were found to be identical with standards given in analytical profile of drug substance.

Melting point determination

Drug	Melting point (˚C)
Ketoprofen	71-75°C

Table 7: Melting point of Ketoprofen

The melting point of pure Ketoprofen was found to be 71-15˚C. This was found to be identical with the standardas given in analytical profile of drug.

Solubility determination

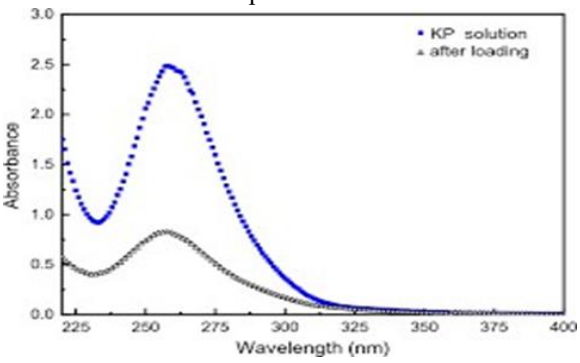
Sr. No.	Solvent	Solubility (Mean ± S. D.)
1	In distilled water	0.025±0.001mg/ml
2	In Phosphate buffer (pH 7.4)	50.2±5.0 mg/ml
3	In Methanol	120±5.0 mg/ml

Table 8: Solubility profile of Ketoprofen

The solubility of Ketoprofen in distilled water was found to be 0.025±0.001mg/ml, which indicates that Ketoprofen is practically insoluble in distilled water. 50.2±5.0 mg/ml, solubility of Ketoprofen in Phosphate buffer (pH 7.4) indicates that it is Soluble in Phosphate buffer (pH 7.4). And the solubility of Ketoprofen in methanol was found to be 120 mg/ml, which indicates that ketoprofen is freely soluble in methanol.

Determination of λ max of ketoprofen

The λ max of ketoprofen found to be 256nm



Spectroscopic studies.

Preparation of standard calibration curve of ketoprofen in phosphate buffer (pH 7.4)

Sr. No.	Concentration (ug/ml)	Absorbance
1	0	0
2	5	0.1476
3	10	0.3292
4	15	0.4892
5	20	0.6456
6	25	0.8211
7	30	0.9791

Table 9: Calibration Curve of ketoprofen in phosphate buffer (pH 7.4)

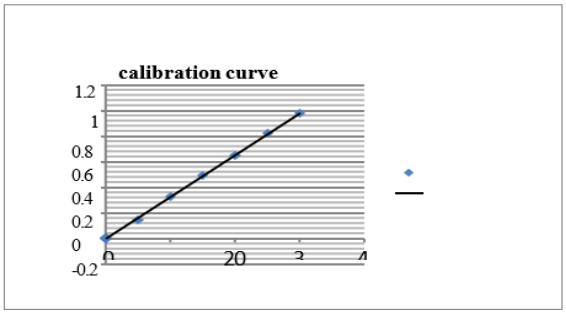


Figure 10: Calibration curve of pure ketoprofen drug

From the equation of line of calibration curve of ketoprofen in phosphate buffer (pH 7.4), the slope was found to be 0.0329 and with intercept 0.0055. And correlation coefficient (R^2) was found to be = 0.999. The value indicates that the calibration curve of pure Ketoprofen was found to be linear.

Compatibility study: FT-IR study

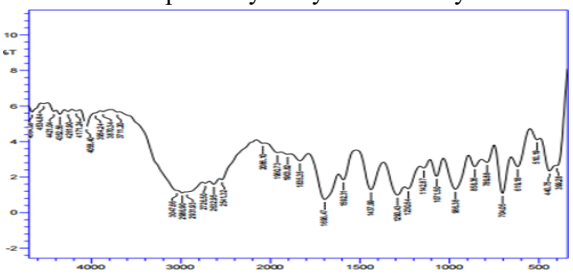


Figure 11: FT-IR spectrum of pure Ketoprofen

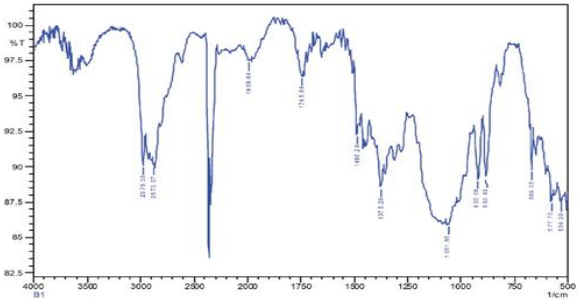


Figure 12: FT-IR spectrum of ethyl cellulose

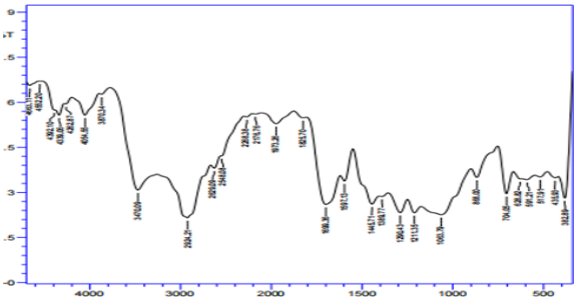


Figure 13: FT-IR spectrum of Physical mixture ketoprofen + ethyl cellulose

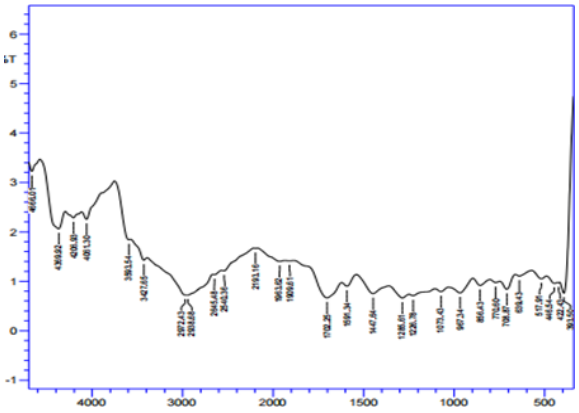


Figure 14: FT-IR spectrum of Physical mixture of ketoprofen +Eudragit E100

Evaluation of Ketoprofen Microspheres

Batch No.	Percentage yield (%)	Particle size (um) (Mean ± S. D.) n=100	Drug content (%)
F1	66.46%	4.2±0.52	91.92
F2	78.54%	5.1±0.61	94.55
F3	69.36%	6.0±0.63	89.64
F4	46.23%	7.2±0.52	75.89
F5	57.68%	5.1±0.61	79.71
F6	51.76%	3.2±0.52	77.52
F7	56.97%	5.1±0.61	61.57
F8	68.23%	3.2±0.52	64.97
F9	49.22%	4.2±0.52	57.96

Table 10: Evaluation of Partical Size, yeild, Drug Content

From the above study we get the result as such the Percentage Yield (%) of the various batchs shown that low 46.23% To high 78.54% as the F2 batch shows the highest yield 78.54%, the Particle size (um)of various

All the characteristic peaks of Ketoprofen were present in the spectrum of drug and physical mixture, indicating compatibility between drug and polymer. The spectrum confirmed that there is no significant change in the absorption bands, hence no interaction was observed between them. However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. yield, Drug Content batchs shown that low 3.2±0.52 to high 7.2±0.52 as F2 batch shows highest partical size 7.2±0.52 and the Drug content% of varioyus batchs shown low 57.96 To high 94.55%as F2 batch shown the highest 94.55.

Micromeritic studies of Microspheres

Batch No.	Bulk Density gm/cc	Tapped Density gm/cc	Carr's index (%)	Hausner's ratio	Angle of Repose °
F1	0.19	0.21	0.04	1.10	23.22
F2	0.25	0.27	0.07	1.08	21.80
F3	0.22	0.24	0.08	1.09	22.29
F4	0.23	0.25	0.08	1.08	23.26
F5	0.25	0.29	0.13	1.16	26.56
F6	0.23	0.27	0.14	1.17	27.47
F7	0.22	0.26	0.15	1.18	28.16
F8	0.20	0.24	0.16	1.2	29.59
F9	0.21	0.26	0.19	1.23	29.80

Bulk density =0.19 to 0.25
Tapped density =0.21 to 0.29
Compressibility index = 0.04 to 0.19
Hausner's ratio = 1.2 to 1.23

Angle of repose= 21.80 to 29.80, respectively powder is considered to have
excellent flow properties. As per the result shows that the from F1 To F4 batch it shows Excellent flow property & From F5 To F9 Batch shows good flow property.

In-vitro dissolution study

Time (min)	Percentage of drug release (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	12.28	13.73	13.01	11.16	12.62	12.32	11.52	12.10	11.01
2	22.43	28.22	25.75	22.39	23.12	22.39	24.56	24.95	24.14
3	31.82	41.70	32.72	34.74	36.19	35.55	34.48	35.63	31.93
4	44.23	45.16	43.59	43.83	43.83	42.07	44.70	43.76	36.67
5	69.81	49.09	48.57	57.94	52.39	47.63	56.62	51.44	44.98
6	72.26	55.50	52.54	70.98	59.57	53.76	60.95	57.54	50.23
7	77.25	61.12	59.44	75.50	62.75	56.34	69.53	62.76	55.35
8	81.11	69.03	68.85	81.18	66.56	59.39	72.54	70.98	59.49
9	85.12	72.52	73.17	87.24	73.37	72.91	79.02	73.41	65.89
10	90.36	79.64	79.65	89.33	75.50	74.74	80.34	78.34	68.76
11	-	86.72	87.00	92.34	83.38	82.66	93.12	85.47	75.56
12	-	97.36	95.24		90.65	88.76	93.44	87.55	81.84

Angle of repose= 21.80 to 29.80, respectively powder is considered to have
excellent flow properties. As per the result shows that the from F1 To F4 batch it shows Excellent flow property & From F5 To F9 Batch shows good flow property.

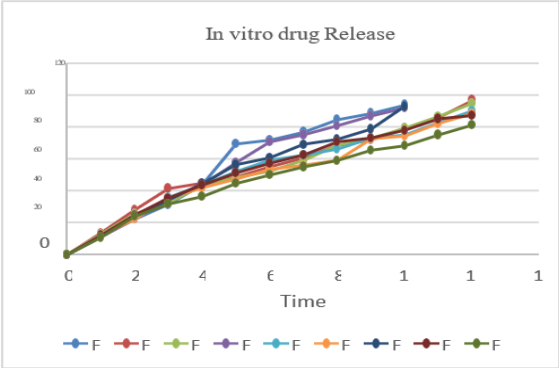


Table 12 & Figure 15 comparison of percentage cumulative drug release profile of formulation

All the batches shown the release between range from F1 Batch shown 12.28 -94.36 F2 Batch shown 13.73 -97.36, F3 Batch shown 13.01 -95.24 F4 Batch shown 11.16-92.34, F5 Batch shown 12.62-90.65, F6 Batch shown 12.32-88.76 F7 Batch shown 11.52-93.45, F7,8 Batch shown 12.10-87.55, and F9 batch shown 11.01 -81.84, hence, F2 Batch shown the maximum release of drug is 97.36 as compared to others.

Kinetics of in vitro drug release

The in vitro drug release data of all the Ketoprofen microspheres formulations and the drug- was subjected to the goodness of fit test by linear regression analysis according to zero order and first orders kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain mechanism of drug release

Formulation	Drug release kinetics				
	Zero-order R2	First order R	Higuchi R	Peppas	
				R2	n
F1	0.4704	0.249	0.9543	0.602	0.278
F2	0.432	0.2622	0.9618	0.6285	0.277
F3	0.4891	0.2172	0.9077	0.6196	0.288
F4	0.8862	0.0074	0.9539	0.8735	0.302
F5	0.8226	0.0332	0.8859	0.7177	0.314
F6	0.7788	0.044	0.9548	0.8992	0.297
F7	0.7431	0.0688	0.9439	0.7374	0.293
F8	0.7628	0.0678	0.9372	0.7106	0.271
F9	0.7266	0.0808	0.9696	0.737	0.221

Table 13: Kinetics of in vitro drug release

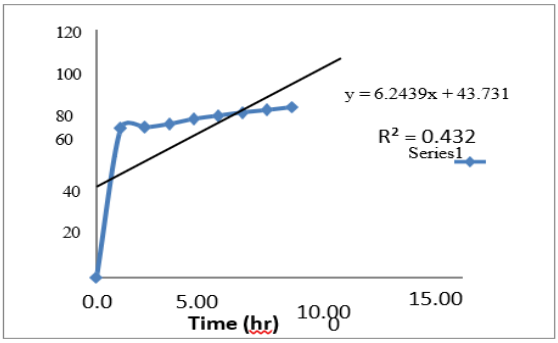


Figure 16: Zero-order release kinetics profile of optimized formulation F2

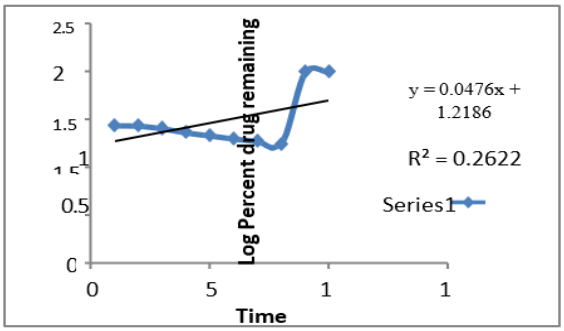


Figure 17: First order release kinetics profile of optimized formulation F2

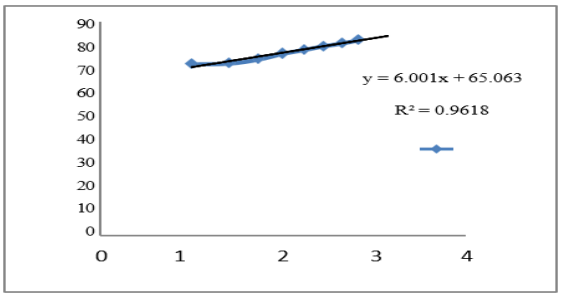


Figure 18: Higuchi release kinetics profile of optimized formulation F2

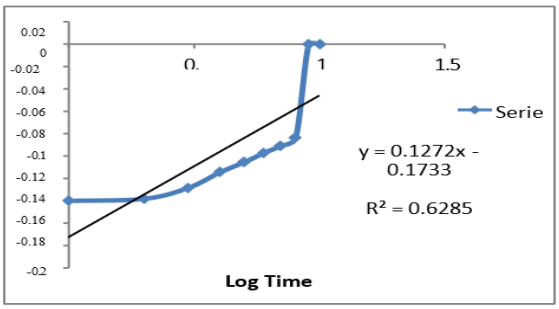


Figure 19: Peppas release kinetics profile of optimized formulation F2

As the kinetics profile release shown that the value which we get R^2high in 0.9618 in higuchi release shown that it is a sustain release drug.

Scanning Electron Microscopy:

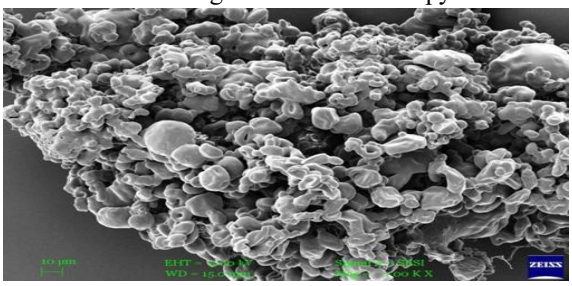


Figure 20: Maginification at 1.00kx

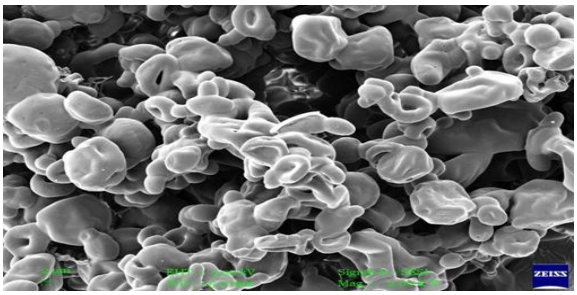


Figure 21: Maginification at 2.00kx

By Scanning electron microscopy, the surface morphology of microspheres study. The sample was observed under scanning electron microscopy at 1,2 KX magnetic resonance. The SEM images of batch F2 confirms that microspheres were spherical in size with no drug crystal on the surface of Microspheres.

Stability studies

The formulation batch F2 analyzed for drug content and in- vitro release studies. The results are given below:

a) Drug content after stability study

The drug content of optimized batch after stability study was found to be 93.62±0.23%.

Optimized batch	Drug content before stability	Drug content after stability
F2	94.55	93.62

Table 14: Drug content after stability study

b) In-vitro drug release study after stability

Time (min)	Before stability (0 Days) F2	After stability (30 days)	After stability (60 days) F2
0	0	0	0
1	13.73	12.43	11.01
2	28.22	27.45	26.01
3	41.70	40.66	39.34
4	45.16	44.11	43.09
5	49.09	48.06	47.01
6	55.50	54.44	54.23
7	61.12	60.11	59.01
8	69.03	68.01	67.01
9	72.52	71.50	70.44
10	79.64	78.55	77.24
11	86.72	85.21	84.01
12	97.36	96.10	95.01

Table 15: In- vitro release studies Before and After Stability

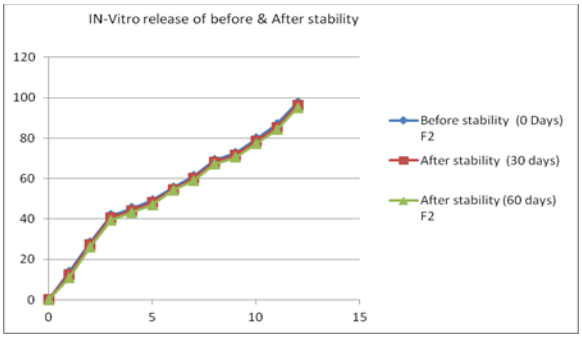


Figure 22: Drug release of before After stability.

There were no physical changes in appearance and melting point. after subjecting formulation to the stability studies, the result was shown that there were no major changes in drug content and in In vitro drug release, hence the formulation was found to be stable.

VII. CONCLUSION

Using the right spray drying technological parameters, ketoprofen microspheres based on ethyl cellulose, Eudragit RS100, Eudragit Rl100, and Eudragit E10 blend can be produced by spray drying with good production yields, high drug content, and encapsulation efficiency. Every formulation has a limited size distribution, a smooth surface, and a spherical shape, all of which are favorable morphological and dimensional features. Ethyl cellulose can be used as a rate retardant material in a 1:2 ratio with ketoprofen to achieve a sustained release.

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