Formulation And Evaluation of Microspheres by Using Spray Drying Technique

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Abstract—**Ketoprofen is one noninflammatory drug (NSAID). drug belongs to the class of NSAIDs.The work plan has been divided into different portions because it is a BCS class II medicine. First obtaining theoretical information by conducting a pharmacological profile and literature study. The next step was to acquire materials and standardize them. To ascertain the color, taste, flavor, and melting point of the drug, reformulation studies were carried out.**

The findings demonstrated that these attributes matched those listed in the medication material's analytical profile. The compatibility examination utilizing FTIR spectroscopy and an FTIR spectrophotometer revealed no interaction between the medication and carrier.

The ketoprofen microspheres were made by spray drying ethyl cellulose, Eudragit RS, Eudragit RL, and Eudragit E100 as rateretarding polymers. The generated formulations were evaluated using a range of metrics, such as practical yield, micromeritic analysis, particle size measurement, drug content, invitro drug release, scanning electron microscopy (SEM), and stability studies. SD showed better flow properties, according to the micromeritic analysis. Furthermore, it was shown that the techniques employed in this work to produce spray dried microspheres may produce a formulation with a constant drug content. By using in vitro sink conditions with the proper dissolving media, we can gain additional insight into how the medication will function inside the body.

Alongside the dissolution research, two aspects are looked at: the amount of drug solubilized and the pace of dissolution. The invitro study found that an increase in carrier concentration speeds up the rate of dissolution. A faster rate of disintegration was observed in the order of A good solubility profile depends on the drug staying in its amorphous form in the formulation, which stability tests guarantee. Following two months of stability testing at 40ºC and 75% relative humidity, the drug content and dissolution of the selected optimal formulation were evaluated. The findings of the alter analysis showed no significant changes in the physical appearance, drug content, or in vitro drug release.

I. INTRODUCTION

The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug foran extended period of time.This is typically accomplished by attempting to obtain "zeroorder" release from the dosage form. Zero order release, or a constant release rate, is the release of medication from the dosage form that is independent of the amount of drug in the delivery system. Sustained release systems, which try to mimic zeroorder release by giving the drug gradually in a firstorder way (i.e., concentration release dependent), usually fail to produce this type of release. Systems that are categorized as prolonged release might also be thought of as efforts to accomplish sustained release delivery. Sustained release (SR), sustained action, prolonged action, protracted action, and retarded release are only a few of the oral extended-release rate dosage forms that have been dubbed "controlled-release pharmacological formulations." These words were first used by pharmaceutical companies to describe extended release (ER) dosage forms either as a marketing term or to denote a special design for an ER dosage form.

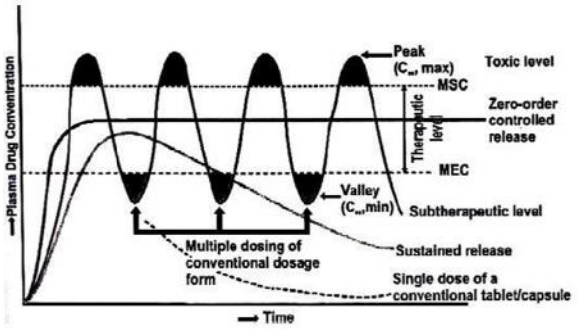


Figure 1: A hypothetical plasma concentration vs time profile from conventional. multiple and single doses of sustained release drug delivery formulations.

Advantages
• Dosing less frequently • Minimal fluctuations in blood medication levels • Improved convenience and patient adherence • Avoid taking medication at night. • A reliable therapeutic result • Increased bioavailability (for some drugs) • Lower medical costs Disadvantages • A possible decline in systemic accessibility • A weak link between in vivo and in vitro • Drug retrieval in toxicity is challenging; there is a possibility of dose dumping.

A. Physicochemical Properties
• The dosage
• Water solubility and pKa
• Drug stability the molecules' size and diffusivity • Protein binding

B. Features of Biology
• Absorption rate
• The allocation
• The process of metabolism
• Half-life and removal

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 are defined as spherical particles (11000 μm) made of biodegradable or synthetic polymers in which the drug is distributed within a polymer matrix. Common polymers include albumin, gelatin, chitosan, starch, sodium alginate, and polylactic acid (PLA), polyglycolic acid (PGA), and cyanoacrylates.

Advantages of microspheres include:
• controlled and targeted drug delivery;
• improved bioavailability;
• protection from moisture, oxygen, and light;
• enhanced stability;
• improved handling of liquids and toxic substances;
• prolonged release dosage forms;
• enteric-coated delivery

Microsphere Preparation Techniques:
1. The method of protein gelation 2. The single emulsion technique 3. The double emulsion technique 4. The multiple emulsion technique 5. Evaporation of solvents
6. Sonication
7. Drying with a spray
8. Congealing spray 9. Coacervation, or phase separation 10. Methods of polymerization 11. Extraction of solvents Principle of Spray Drying Technique Dry microspheres are collected after the liquid input is atomized into droplets, exposed to hot air, and the solvent evaporates.

II MATERIALS AND METHODS

Materials

The drug, excipients, chemicals/ reagents used for various experiments are enlisted as follows.

Sr. No	Name of material	Manufacturer/ Supplier
1	Ketoprofen	Swapnroop Drugs & Pharmaceuticals, Aurangab Ad.
2	Eudragit RS100	Research lab fine chem Industries, Mumbai
3	Eudragit RL100	Research lab fine chem Industries, Mumbai
4	Eugdragit E100	Research lab fine chem Industries, Mumbai
5	Methanol	SD Fine chem. Limited, Mumbai
6	Sodium Hydroxide	Research lab fine chem Industries, Mumbai
7	Potassium Dihydrogen Phosphate (PDP)	Merck Specialities Private limited, Mumbai
8	Phosphate buffer (pH 7.4)	Merck Specialities Private limited, Mumbai

Table 1: List of materials used during experiment

Preformulation Studies of Ketoprofen
Organoleptic Evaluation
Ketoprofen was characterized for its organoleptic properties, including appearance, colour, odour, and taste. Approximately 2 g of the drug was uniformly spread on a clean white sheet of paper and visually examined for its appearance. A small quantity of ketoprofen powder was placed on butter paper and observed under adequate illumination to determine its colour. The drug appeared as a white to off-white, non-

hygroscopic, fine-to-granular powder. The odour was assessed manually and found to be odourless. The reported melting point of ketoprofen is approximately 95°C.

Melting Point Determination

The melting point of ketoprofen was determined using the capillary tube method with a melting point apparatus. A capillary tube was filled with a small amount of drug by gently pressing its open end into the sample and tapping the bottom of the tube to compact the powder. The filled capillary tube was placed in the apparatus, and the temperature was gradually increased. The temperatures at which the drug began to melt and completely melted were recorded.

Solubility Studies

The solubility of ketoprofen was evaluated in various solvents to determine its dissolution characteristics. An excess amount of the drug was added separately to test tubes containing 3 mL of different solvents, including methanol, ethanol, acetone, chloroform, distilled water, 0.1 N hydrochloric acid, and phosphate buffer (pH 7.4). The tubes were tightly closed and shaken in a water bath shaker for 24 hours at room temperature to achieve equilibrium. After incubation, the samples were centrifuged at 15,000 rpm, and the supernatant was collected, filtered, and suitably diluted. Drug concentration in each solvent was determined spectrophotometrically at 260 nm.

Drug–Excipient Compatibility Study

The compatibility between ketoprofen and the selected polymers was investigated using Fourier Transform Infrared (FTIR) spectroscopy. Samples of the pure drug and physical mixtures of the drug with polymers were prepared by the potassium bromide (KBr) pellet method. The powdered samples were mixed with KBr, compressed into pellets using a hydraulic press, and analyzed over the spectral range of 4000–400 cm^{-1} with a resolution of 2 cm^{-1}. Compatibility was assessed by comparing the characteristic absorption peaks of the pure drug with those of the physical mixtures to identify any significant peak shifts or disappearance, indicating possible drug–excipient interactions.

Spectroscopic Analysis of Ketoprofen

Preparation of Standard Calibration Curve

A calibration curve of ketoprofen was prepared in phosphate buffer (pH 7.4) for quantitative spectrophotometric analysis.

Preparation of Stock Solution

An accurately weighed quantity of 10 mg of ketoprofen was dissolved in phosphate buffer (pH 7.4), and the final volume was adjusted to 100 mL to obtain a stock solution containing 100 µg/mL of the drug.

Preparation of Standard Solutions

Aliquots ranging from 0.5 to 5.0 mL of the stock solution were transferred into separate 10 mL volumetric flasks and diluted to volume with phosphate buffer (pH 7.4), producing concentrations between 5 and 50 µg/mL. The absorbance of each solution was measured at 260 nm against phosphate buffer as the blank. A calibration curve was constructed by plotting absorbance against drug concentration.

Preparation of Spray-Dried Ketoprofen Microspheres

Spray-dried microspheres containing ketoprofen were prepared using different polymeric carriers by the spray-drying technique under optimized operating conditions.

Formulation with Ethyl Cellulose

The required quantities of ketoprofen and ethyl cellulose, according to the formulation design, were dissolved in methanol to obtain a homogeneous solution. The solution was continuously stirred using a magnetic stirrer during spray drying. The feed solution was processed using a co-current spray dryer under predetermined operating conditions to produce ketoprofen-loaded ethyl cellulose microspheres.

Formulation with Eudragit E100

Ketoprofen and Eudragit E100 were accurately weighed according to the formulation composition and dissolved in methanol. The resulting solution was continuously stirred to maintain homogeneity throughout the spray-drying process. Spray drying was performed in co-current mode under optimized process parameters to obtain microspheres.

Formulation with Eudragit RS100 and Eudragit RL100

For combination polymer formulations, accurately weighed quantities of ketoprofen, Eudragit RS100,

and Eudragit RL100 were dissolved in methanol. The polymeric solution was stirred continuously using a magnetic stirrer before and during spray drying to ensure uniform dispersion. Spray drying was carried out in co-current mode using the operating conditions specified in the formulation design to produce ketoprofen-loaded microspheres with controlled-release characteristics.

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 2: 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 3: 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 4: 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

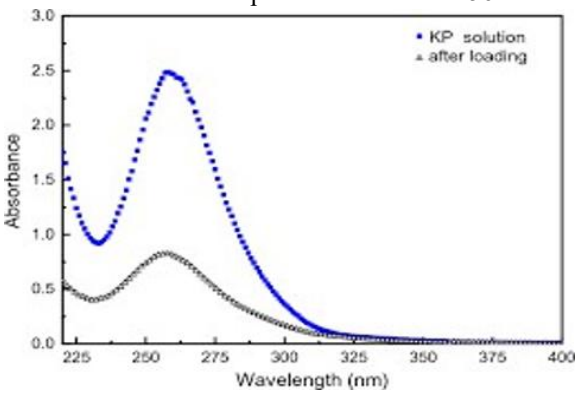
Sr. No.	Solvent	Solubility (Mean ± S. D.)
1	In distilled water	0.025±0.001mg/ml
2	In Phosphate buffer (pH 7.4)	50.2±5.0 mg/ml
3	In Methanol	120±5.0 mg/ml

Table 5: 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 6: Calibration Curve of ketoprofen in phosphate buffer (pH 7.4)

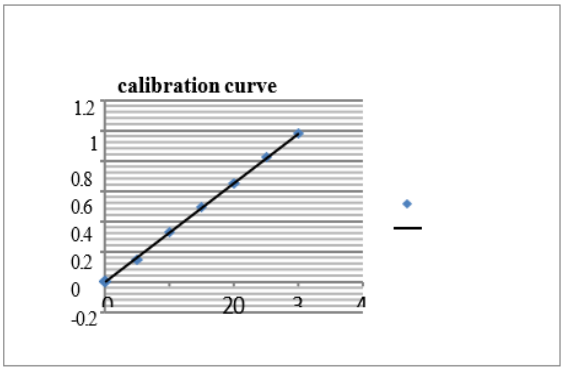


Figure 2: Calibration curve of pure ketoprofen drug

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

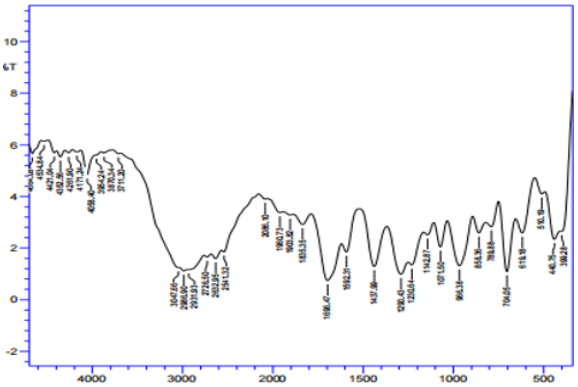


Figure 3: FT-IR spectrum of pure Ketoprofen

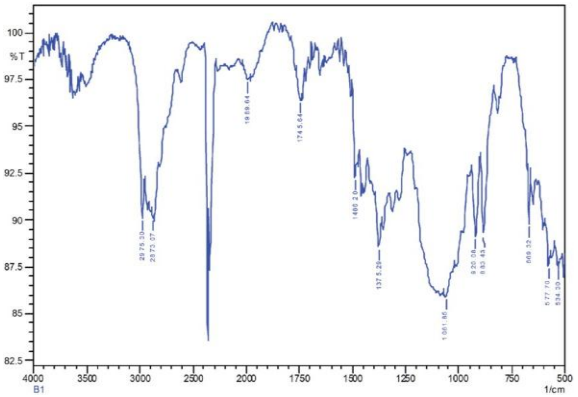


Figure 3: FT-IR spectrum of ethyl cellulose

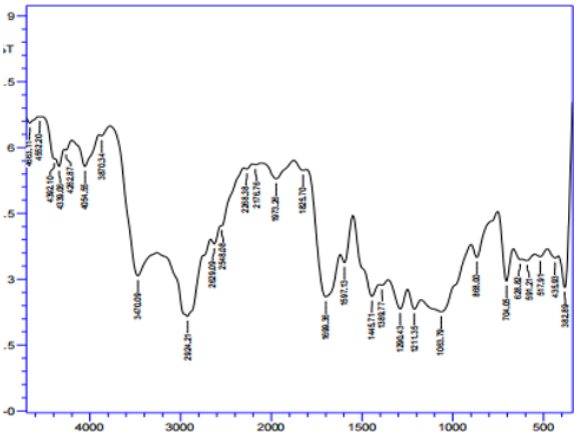


Figure 4: FT-IR spectrum of Physical mixture ketoprofen + ethyl cellulose

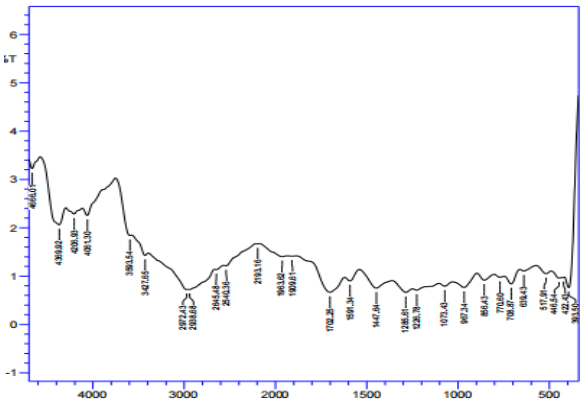


Figure 5: FT-IR spectrum of Physical mixture of ketoprofen +Eudragit E100

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.

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 7: 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 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

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.

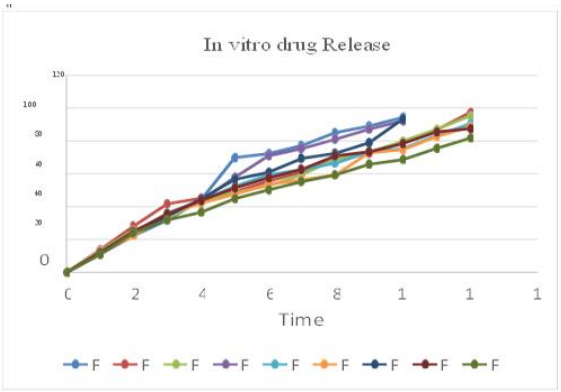


Table 7 & Figure 6 comparison of percentage cumulative drug release profile of formulation

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 8: Kinetics of in vitro drug release

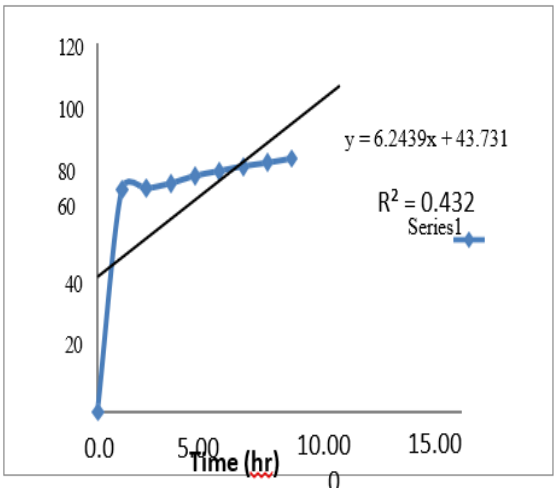


Figure 7: Zero-order release kinetics profile of optimized formulation F2

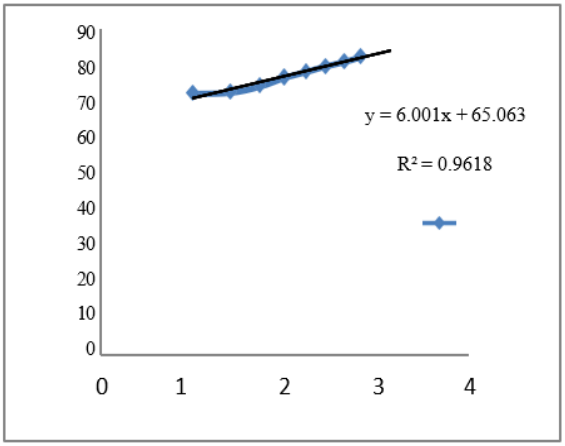


Figure 9: Higuchi release kinetics profile of optimized formulation F2

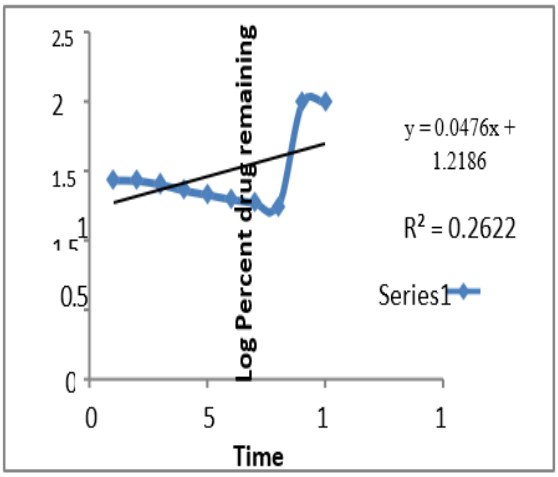


Figure 8: First order release kinetics profile of optimized formulation F2

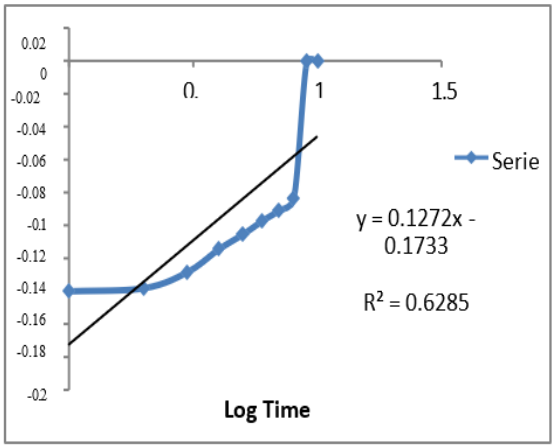


Figure 10: Peppas release kinetics profile of optimized formulation F2

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

Scanning Electron Microscopy:

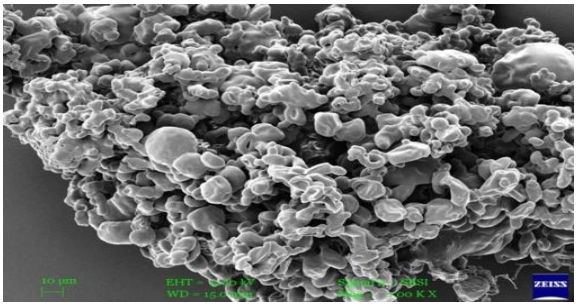


Figure 11: Maginification at 1.00kx

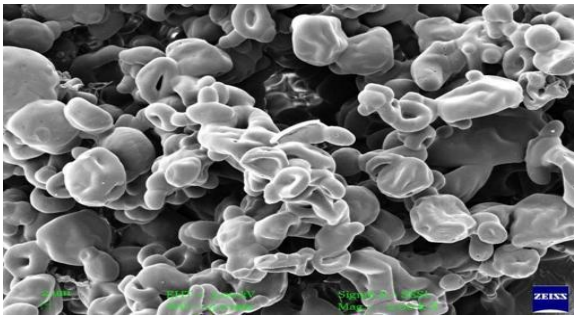


Figure 12: Maginification at 2.00kx

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 9: 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 10: In- vitro release studies Before and After Stability

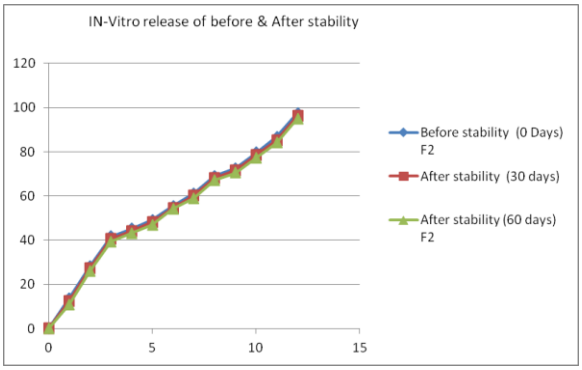


Figure 13: Drug release of before After stability.

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.

IV. CONCLUSION

The study demonstrates that ketoprofen-loaded microspheres can be successfully prepared using the spray-drying technique by optimizing the processing parameters. Microspheres formulated with polymers such as ethyl cellulose, Eudragit RS100, Eudragit RL100, and Eudragit E10 blends showed excellent manufacturing performance, characterized by high production yield, high drug loading, and efficient drug encapsulation. These results indicate that spray drying is a reliable and effective method for producing controlled-release ketoprofen microspheres.

Morphological evaluation revealed that all formulations possessed desirable physical characteristics. The microspheres exhibited a narrow particle size distribution, ensuring uniformity among particles, along with a smooth surface and spherical

shape, which are beneficial for improved flow properties, better stability, and reproducible drug release behavior.

Among the polymers investigated, ethyl cellulose proved to be the most effective release-retarding material. When used in a 1:2 ketoprofen-to-ethyl cellulose ratio, it successfully prolonged the release of ketoprofen, resulting in a sustained-release formulation. The hydrophobic nature of ethyl cellulose slows the penetration of dissolution medium into the microspheres, thereby controlling the diffusion of the drug and extending its release over time.

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