Journal of Advanced Zoology

ISSN: 0253-7214
*Volume **44** Issue **S-5 Year 2023** Page **2227:2237***

Formulation and Evaluation of Lornoxicam Nanosuspension with Eudragit Rs100 Polymer

Sunil Aher[1*], Poonam Patil[2], Kiran Mahajan[3], Smita Kumbhar[4], Puja Saha[5], Sheetal Samant[6], Niravsinh Rathod[7]

[1]*Department of Pharmaceutics, SRES's Sanjivani College of Pharmaceutical Education and Research, Kopargaon, MS, India-423603.*
[2]*Department of Pharmaceutical Chemistry, SRES's Sanjivani College of Pharmaceutical Education and Research, Kopargaon, MS, India-423603.*
[3]*Department of Pharmaceutics, SGMSPM's Sharadchandra Pawar of College of Pharmacy, Dumbarwadi (Otur), Tal- Junnar, Dist- Pune, Maharashtra, India 410504.*
[4]*Department of Pharmaceutical Analysis, D.S.T.S. Mandal's College of Pharmacy, Solapur, Maharashtra, India, 413004.*
[5]*Department of Pharmaceutics, Mata Gujri College of Pharmacy, Mata Gujri University, Kishanganj, Bihar, India, 855107.*
[6]*Department of Pharmacognosy, Yashwantrao Bhonsale College of Pharmacy, Sawantwadi, Maharashtra India, 416510.*
[7]*Department of Pharmaceutics, Parul Institute of Pharmacy, Parul University, Vadodara, Gujrat,391760*

**Corresponding author's E-mail: suniljaher@gmail.com*

Article History

Received: 06 June 2023
Revised: 05 Sept 2023
Accepted: 14 Nov 2023

Abstract

BCS Class II has a low aqueous solubility problem in pharmaceutical formulation. Hence to overcome this problem this research the was carried out for BCS Class II drug lornoxicam was selected to enhance the aqueous solubility by formulating nanosuspension with a polymer like Eudragit RL100, Eudragit RS100 and Poloxamber407 as a stabilizer. The present study focuses on the polymer Eudragit RS100. A total of four formulations LRS-F1, LRS-F2, LRS-F3, LRS-F4, and LRS-F4 were prepared with a ratio of drug: polymer: stabilizer (1:1:0.5 & 1:2:0.5, 1:1:1 & 1:2:1)LRS-F4 formulation was found to be optimized formulation with 90.00 – 100 nm particle size & -11.20 zeta potential and % drug release at the end of 10 hrs was found to be 96.88 % with the increase in the dissolution/saturation solubility of 70.36±0.09 (µg /mL) of poorly water-soluble lornoxicam (reported solubility with 14.28 µg /mL µg /mL). The amount unincorporated was found to be 09.74 % with an optimized formulation. Moreover, the physical appearance of the nanosuspension was found to be up to the mark confirming that the nanosuspension is stable and has no crystal growth or crystal development with optimized formulation at a temperature of 4 °C for 3 months. Poloxamer 407 as a stabilizer.

Keywords: *Nanosuspension, Meloxicam, Quassi emulsification solvent diffusion, Class II drug, solubility Enhancement, bioavailability.*

1. Introduction

One of the predominant limitations to the improvement of tremendously mighty pharmaceutics is the terrible water solubility of many drugs. Approximately 40% of capacity new drugs recognized with the aid of pharmaceutical companies are poorly Water soluble, which significantly hinders their medical translations [1]. Nanosuspensions are aqueous suspensions containing one or numerous submicron-sized drug materials and suitable stabilizers. Stabilizers consist of excipients that permit nano grinding of the drug particles, save you crystal boom or nanoparticle aggregation at some stage in storage, pH-buffering materials, preservatives, and different additives that can be wished for similar processing or management to patients (e.g., sweeteners, colorants) [2,3]

Preparation Of Nanosuspensions

The different techniques are used to prepare nanosuspension these are as follows

Bottom-up Technology

Bottom-up technology is used for the preparation of nanosuspension and is called an ancient method. In this method, the first drug is dissolved in a nonaqueous phase or solvent and then this solution is mixed with an aqueous solvent. As the drug aqueous solubility is low then the drug particles will start to precipitate and this is carried out by stirring. The Nano-edge process relies on the precipitation of the friable materials for subsequent fragmentation under conditions of high-speed stirring or high shear and/or thermal energy [4]. And this is given or accomplished by a combination of high-pressure homogenization and rapid precipitation. The rapid addition of the drug solution to an anti-solvent (like organic to water) then will produce a sudden supersaturation of particles of the mixed solution which results in the generation of crystalline i.e., fine crystals or amorphous solids. Precipitation of amorphous material may favor at high supersaturation & then the solubility of the amorphous state is exceeded.

Top-down Technology

a) High-pressure homogenization: this method is used for the improvement of water solubility of the water-insoluble drug [5]. In the method, the suspension of a drug & surfactant is forced through a nano-sized aperture valve of a high-pressure homogenizer. This method principle depends on the cavitation in the aqueous phase. In this method, the particle cavitation forces are maximum or high in order to convert the drug from microparticles to nanoparticles or nanosuspension. In the High-Pressure Homogenization method, there is the requirement for small sample particles before putting or incorporating and the actual / fact and many cycles of high-speed homogenization are needed or required. R.H. Muller developed a technology of dissocubes technology. It is the technology that uses a piston-gap-type of high-pressure homogenizer which was patented recently and was owned by Skye Pharm [6,7]

Nanosizing refers to the reduction of the active pharmaceutical ingredient (API) particle size down to the sub-micron range. While reduction of particle size has been employed in the pharmaceutical industry for several decades, recent advances in milling technology and our understanding of such colloidal systems have enabled the production of API particles of 100–200 nm size in are producible manner. The sub-micron particles are stabilized with surfactants or polymers in nanosuspensions which can be further processed into standard dosage forms, such as capsules or tablets, suitable for oral administration. These nanoformulations offer increased dissolution rates for drug compounds and complement other technologies used to enhance the bioavailability of insoluble compounds (BCS Class II and IV) such as solubility enhancers (i.e., surfactants), liquid-filled capsules or solid dispersions of drugs in their amorphous state. The advantages of nanoformulations in oral drug delivery have been demonstrated in vitro in dissolution testing and in vivo in both preclinical studies as well as clinical trials. Nanocrystalline API has been shown to dramatically increase the rate of dissolution in vitro improve bioavailability, reduce variability, and alleviate positive food effects for orally administered drug molecules [8,9]

Formulation Considerations

A) Stabilizer

Nanosuspension is biphasic and the stabilizer has an important role in the stabilization of the formulation. The high surface energy of reduced or nanosized particles can be induced if there is an absence of the stabilizer and the particle will agglomerate or there will be the aggregation of the drug particle or drug crystals will take place.

B) Organic solvents

If nanosuspension is prepared through or by using the microemulsion or emulsion as a template, the organic solvent is required. As these techniques are still in their infancy, to elaborate information on formulation considerations is not available. The acceptability of the organic solvents in the pharmaceutical, their toxicity potential, and the ease of their removal from the formulation need to be considered when formulating nanosuspensions using emulsions or microemulsions as templates. Partially water-miscible organic solvents like glycols can be used as the internal phase of the microemulsion when the nanosuspensions are to be produced using a microemulsion as a template.

C) Surfactants

Surfactants are surface active agents used to alter the surface or interfacial properties. (reducing the surface tension or interfacial tension) So in the dispersion they are added to improve the dispersion by minimizing or reducing the interfacial tension. Surfactants also have applications like wetting, spreading, and deflocculating properties e.g. such as tween etc are used as surfactants.

D)Co-surfactants

Formulation of nanosuspension from the microemulsion then the choice of cosurfactant is critical one. As the cosurfactant can affect phase behavior and also the uptake of the internal phase which is selected for the microemulsion composition with the drug loading that should be found or investigated as like e.g., Transcutol, glycofurol, ethanol, and isopropanol - safely used as co-surfactants. Other examples used as co-surfactants are bile salts, dipotassium glycyrrhizinate, etc.

E) other additives:

In the nanosuspensions some of them are as Buffers, surfactant, salts, polyols, osmogent, cryoprotectant, the additive added in the formulation varies with the route of administration as well as the properties of the drug.[10].

2. Materials And Methods

Materials

Lornoxicam and Poloxamber407, Eudragit RS 100 and all chemicals required for research study used as AR grade and were purchased from Yarrow chemicals Mumbai, Maharashtra

Methods

Preparation of Lornoxicam Nanosuspensions

Quassi emulsification solvent diffusion technique and lornoxicam nanosuspension were prepared. The Lornoxicam (8 mg) and EudragitRS100(16:32 mg) were co-dissolved in 5 ml of methanol. The solution was to be slowly injected with a syringe containing a thin Teflon tube into 20 ml water containing stabilizer poloxamber 407. It was maintained at a low temperature in an ice bath protected from sunlight. During injection, the mixture was stirred well by a high-speed homogenizer at 5500 rpm speeds for 5 hrs. The solution immediately turned into the pseudo-emulsion of the drug and polymer methanol solution in the external aqueous phase. The counter diffusion of methanol and water out of and into the emulsion microdroplets respectively results in the formation of nanosuspension. Formulations were prepared with varying polymer & stabilizer ratio. Overall, four formulations of Lornoxicam were ready with two different polymer Eudragit RS100 with a stabilizer such as poloxamber 407(Pluronic F127) and the formulations were coded as (LRS-F1, LRS-F2, LRS-F3, LRS-F4, LRS-F4) and the information is mentioned in Table 1.[11]

Table no. 1: Polymeric Formulation Batches

Batch	Drug (mg)	Polymer (mg) Eudragit RS100	Surfactant Poloxamer407 (%)	Distilled water (mL)
LRS-F1	8	8	0.5	20
LRS-F2	8	16	0.5	20
LRS-F3	8	8	1	20
LRS-F4	8	16	1	20

Evaluation Of Nanosuspensions

Particle size analysis

All the formulations of the drug Lornoxicam with EudragitRS100 & Stabilizer Poloxamber 407(Pluronic F127) were subjected to particle size determination and the particle size was determined and recorded by using Scanning electron microscopy (SEM) is a method for high-resolution surface imaging. The SEM uses an electron beam for surface imaging. The advantages of SEM over light microscopy are greater magnification and a much larger depth of field. Different elements and surface topographies emit different quantities of electrons, due to which the contrast in an SEM micrograph (picture) is representative of the surface topography and distribution of elemental composition on the surface [10] The Particle size was performed at STIC Cochin, the evaluation was carried out with SEM Make JEOL Model JSM-6390lv.

Zeta potential of the Drug

Zeta Potential was determined to know the stability of the nanosuspension is a very important parameter because the biphasic dosage in form i.e suspension stability depends upon the charge or the total electrical double layer formed around the dispersed nanoparticle. Zeta potential measurements were run at 250C with an electric field strength of 23 V/m, using Zetasizer (Nano ZS 90, Malvern Instruments, UK). To determine the zeta potential, samples of drug nanosuspension were diluted in solvent and

placed in an electrophoretic cell. The zeta potential was calculated as described by the Helmholtz–Smoluchowski equation.

% Entrapment efficiency

In order to determine the % entrapment around 2 ml of each formulation was taken in the Nessler's cylinder tube (10 ml) the solution was centrifuged in the centrifuge machine at 2000-3000 rpm for 4 hrs. The supernatant layer was filtered through Whatmann filter paper number 41and diluted with phosphate buffer 7.4 pH up to 10 ml and the resultant solution was analyzed at the specific wavelength of the drug in nm using a UV Double beam Spectrophotometer-3650.These were carried out for three times and the result was calculated [13]. The Percentage entrapment efficiency was calculated according to the equation or formula:

$$\% EE = \frac{\text{Total dug content} - \text{Free dissolve drug}}{\text{Dug amount used}} \times 100 \quad \text{---equation (1)}$$

Saturation Solubility

Saturation solubility is an important physical property that depends on the temperature and is responsible for the dissolving solvent medium. Saturation solubility of the drug and its formulated dry nanosuspensions were carried out in distilled water which contains 5 mg of the drug. The dry form of nanosuspensions was prepared by taking weight equivalent to 5 mg of drug in 2 ml distilled water taken separately and was kept or allowed to be stirred at constant temperature on the mechanical shaker (37.0 ± 1.0 °C) conduct for 24h. The stirred solution was taken in a test tube and at 10000 rpm it was centrifuged for 15 minutes. The upper layer or supernatants were collected and filtered through a 0.22µm nylon membrane filter (Gelman Laboratory, Mumbai, India), diluted with Phosphate buffer. The absorbance was observed using a UV spectrophotometer. Its solubility was determined at 25°C. Every sample was analyzed in triplicate and the mean values and standard deviations were reported. [14]

In-vitro drug Release studies

In vitro drug release of the drugs Lornoxicam with Eudragit RS100 with stabilizer poloxamber 407(Pluronic F127) nanosuspension was carried out by using USP Dissolution apparatus type 2 (paddle Dissolution Apparatus). 5ml of nanosuspension was taken in a dialysis membrane consisting of a spectrap or membrane (cut-off: 1200Da). This dialysis system was tied to the paddle and the dissolution medium was Phosphate buffer pH 7.4. Dissolution was carried in triplicate for 10 hrs. at 37±10°C temperature and 50rpm speed. At regular intervals of time 1ml of sample from the external medium was taken and replaced with fresh phosphate buffer and all the samples were analyzed at nm of respective drug using a U.V spectrophotometer. [13,14]

Mathematical Dissolution Model for the optimize formulation:

The formulation which shows maximum drug entrap as well as saturation solubility & drug release, and optimum zeta potential which gives the measure of stability formulation was considered as an optimized formulation mathematical model like First order plot, Higuchi Plot, Korseymer peppas Plot and by applying this equation the release pattern was determined. This study gives the pattern of the drug release from the polymeric nanosuspension.[15]

Short term stability

Short-term stability studies were performed on all the optimized formulations for three months stored at two sets of conditions first set at 4°C in the refrigerator and second at 37°C ±2°C ,65 % RH ± 5 %RH (Humidity cabinet make REMI Instrument ltd). The samples were removed at intervals of zero month to three months and evaluated for the in vitro drug analysis. As well as any change in physical appearance is observed.[16]

3. Results and Discussion

In present research work nanosuspension of Lornoxicam were formulated with two polymer RS100 with different combination of drug: polymer: stabilizer by using Quasi emulsion solvent diffusion technique from these four with Eudragit RS100 (F1, F2, F3, F4) with a different combination of drug: polymer: stabilizer i.e., ratio of 1:1:0.5 & 1:2:0.5, 1:1:1 & 1:2:1. Particle size was determined for all the formulations by scanning electron microscopy. It was found that the formulations F4 prepared at 5500 rpm speed for 5 hours with ratio of drug to polymer EudragitRS100 (1:2)and the ratio of stabilizer 1.0 percentage had found nano size particle size prepared 90.00-100 nm with a zeta potential of -11.20 .Even the in vitro drug release shows at 10 hrs. 96.88 % .The F4 formulation was found to be reduce

particle size of 90-100 nm & consider to be optimize formulation with increase in the dissolution/saturation solubility of 70.36±0.09 (µg /mL) of poorly water soluble meloxicam (reported solubility with 14.28 µg /mL µg /mL) being formulated in nano composite in the form of nanosuspension.

Particle Size Distribution Analysis

All the formulation of Lornoxicam with a polymer EudragitRS100 with the stabilizer Poloxamber 407 were determined for the particle size by Scanning electron microscopy (JEOL Model JSM-6390lv) Particle size in the nanosuspension is important because as the particle size reduce there is increase in the surface area which will result in the increase in the dissolution rate. As the particle goes in the nano more improving the dissolution of the poorly water-soluble drug. The particle size distribution of formulation F1, F2, F3, F4 these formulate with Eudragit RS100 with varying proportion of Lornoxicam: Eudragit RS100: poloxamber407 was found to be in between 90.00 to 240 nm. And the optimize formulation F4 the particle size was 90.00 – 100 nm. The data was mentioned in table No 2.

Table No.2:

Drug	Particle size(nm)
LRS-F1	150-170
LRS-F2	200-230
LRS-F3	225-240
LRS-F4	90-100

Particle size Study

Amount of Unincorporated Drug

The amount unincorporated was found to 9.74 % with a optimize formulation F4 (Formulated with the Eudragit RS100). The data was mentioned in table No 3

Table No.3: Percentage drug unincorporated and entrapped for nanosuspension

Batches	% Drug Unincorporated	% Drug Entrapped
LRS-F1	11.74	88.26
LRS-F2	14.08	85.92
LRS-F3	19.75	80.25
LRS-F4	09.74	90.26

Zeta Potential

It was found that the formulations F4 prepared at 5500 rpm speed for 5 hours with drug to polymer EudragitRS100 (1:2) and 1% stabilizer had found nano size particle size prepared 90.00-100 nm with a zeta potential of -11.20. The data was mentioned in table No 4.

Table No.4: Zeta potential of Lornoxicam nanosuspension

Sr. no.	Formulation	Zeta Potential(mV)
1	LRS-F1	13
2	LRS-F2	16
3	LRS-F3	10
4	LRS-F4	-11.20

In-vitro drug Release

All the formulation in-vitro drug release study was determined among that F4 found to be optimized. In vitro, drug release shows at 10 hrs. 96.88 % with the particle size of 90-100 nm & considered to be optimized formulation with increase in the dissolution of poorly water-soluble drug being formulated in nanocomposite in the form of nanosuspension. The data was mentioned in Table No 6 and Figure No 1. Statistically dissolution studies applying the Higuchi model and This data was mentioned in Table No 7 and Figure No 2. For First Order Release was used Korsemeyer Pappas model for optimize F2 formulation This data was mentioned in Table No 8,9,10 and Figure No 3,4

Table No.6: Percentage cumulative drug release of Lornoxicam nanosuspension with Eudragit RS100 (LRS-F1 to LRS-F4).

Time (Hrs)	LRS-F1	LRS-F2	LRS-F3	LRS-F4
0	0	0	0	0
1	14	10.62	11.17	19.96
2	21.41	22.77	20.14	30.11
3	31.8	28.14	26.12	38.14
4	44.01	39.44	37.51	47.48
5	52.84	50.17	48.17	56.15
6	61.92	59.13	57.98	68.77
7	75.11	68.81	65.24	76.46
8	81.46	79.33	76.28	88.62
9	89.34	88.79	87.46	90.77
10	93.11	94.22	92.17	96.88

Figure No 1. %Cumulative drug release of Lornoxicam nanosuspension with Eudragit RS100 (LRS-F1 to LRS-F4)

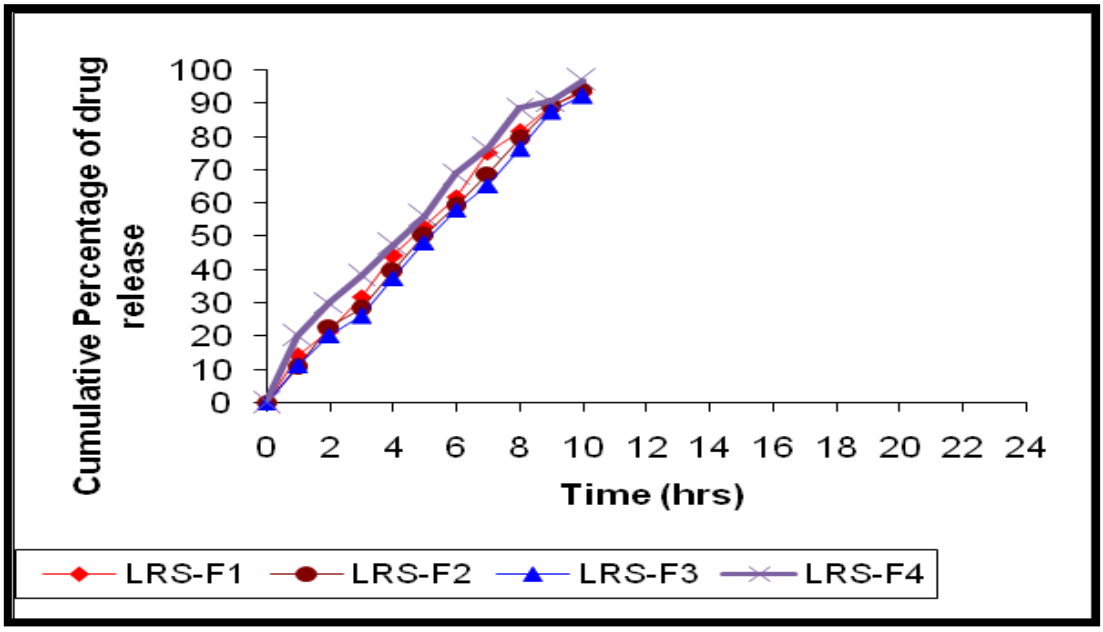


Table No.7: Data for the Higuchi Plot for Optimized formulation LRS-F4

Sr. No	Time	√Time	cumulative %drug release
1	0	0.00	0
2	1	1.00	19.96
3	2	1.41	30.11
4	3	1.73	38.14
5	4	2.00	47.48
6	5	2.24	56.15
7	6	2.45	68.77
8	7	2.65	76.46
9	8	2.83	88.62
10	9	3.00	90.77
11	10	3.16	96.88

Figure No 2. Higuchi Plot for formulation LRS-F4

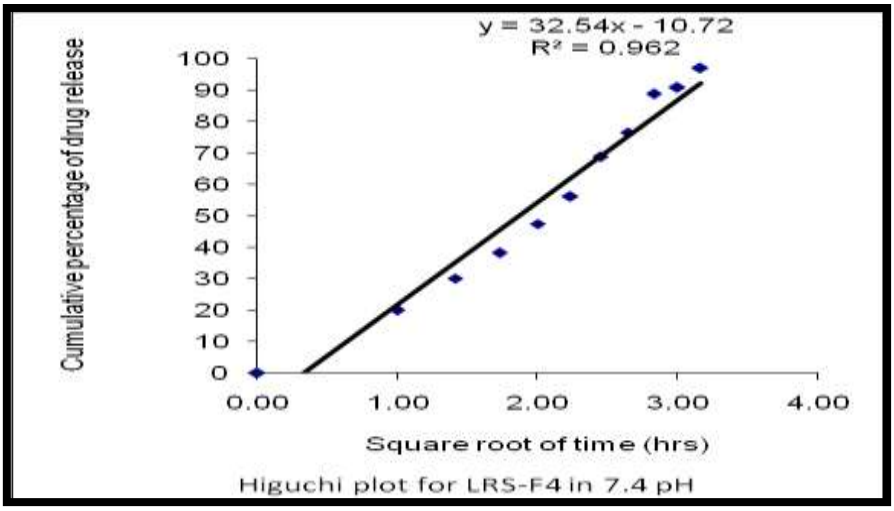


Table No.8: Data of Korseymer Peppas plot for the Optimized LRS-F4 Formulation

korseymer LRS-F4	Time	log time	log cumulative %drug release
1	0	0.00	0.00
2	1	0.00	1.30
3	2	0.30	1.48
4	3	0.48	1.58
5	4	0.60	1.67
6	5	0.70	1.75
7	6	0.78	1.84
8	7	0.85	1.88
9	8	0.90	1.95
10	9	0.95	1.96
11	10	1.00	1.99

Table No.9: Data for first order plot of formulation LRS-F4

Sr. No	Time	Remaining concentration	Log remaining
1	0	100.00	2.00
2	1	80.04	1.90
3	2	69.89	1.84
4	3	61.86	1.79
5	4	52.52	1.72
6	5	43.85	1.64
7	6	31.23	1.49
8	7	23.54	1.37
9	8	11.38	1.06
10	9	9.23	0.96
11	10	3.12	0.49

Figure No 3. Plot of first order of formulation LRS-F4

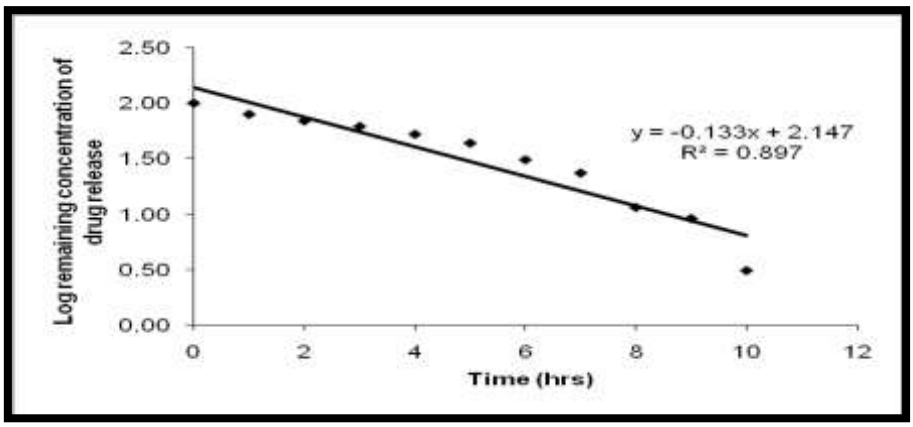
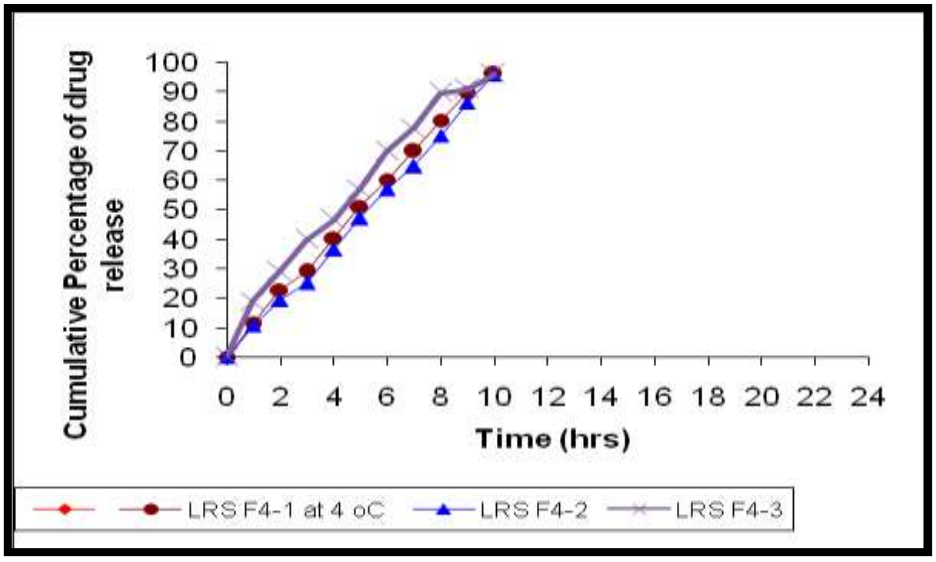


Table no 10: Data of invitro drug release of optimizing formulation ZRS F4 during the stability study at temperature 37 ºC and different interval.

Time (HRS)	ZRS F4 First Month at 37°C	ZS F4 Second Month at 37ºC	ZRS F4 Third Month at 37ºC
0	0	0	0
1	10.14	12.27	16.11
2	22.18	21.17	27.19
3	30.45	32.54	34.13
4	35.17	39.65	40.58
5	41.37	46.89	48.84
6	52.17	58.18	50.42
7	63.23	64.11	59.06
8	73.78	70.01	70.74
9	83.11	76.46	78.53
10	92.43	81.32	80.43

Figure No 4. In vitro drug release of optimize formulation LRS-F4(Lornoxicam) during the stability study at temperature maintained at 4°C for different interval from 0 to 3 months



Compatibility Studies

A. IR Spectra

Raw lornoxicam and polymer Eudragit RS100 Stabilizer Poloxamber 407. IR Spectra was determined which demonstrate the chemical structure with functional group of the drug is not changed as per as compatibility is concerned. The Drug IR spectra was mentioned in Figure no 5. The Compatibility of Drug with Polymer was checked by IR spectra and was shown in figure No 6.

Figure No 5. IR spectrum of Lornoxicam

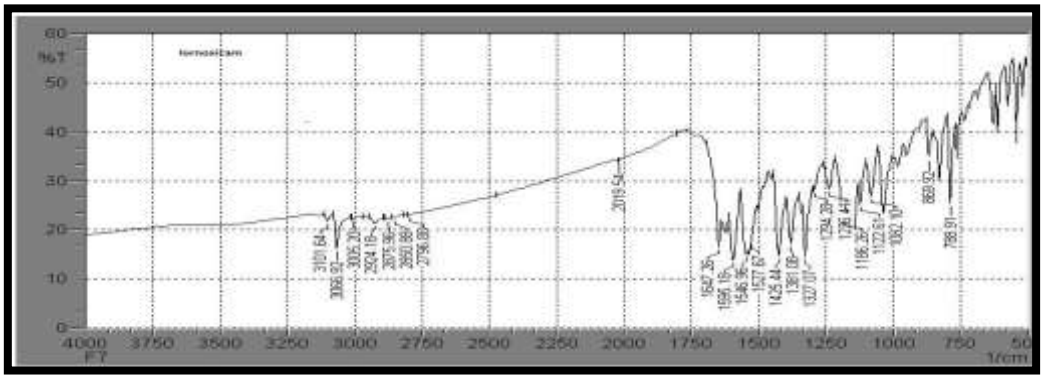
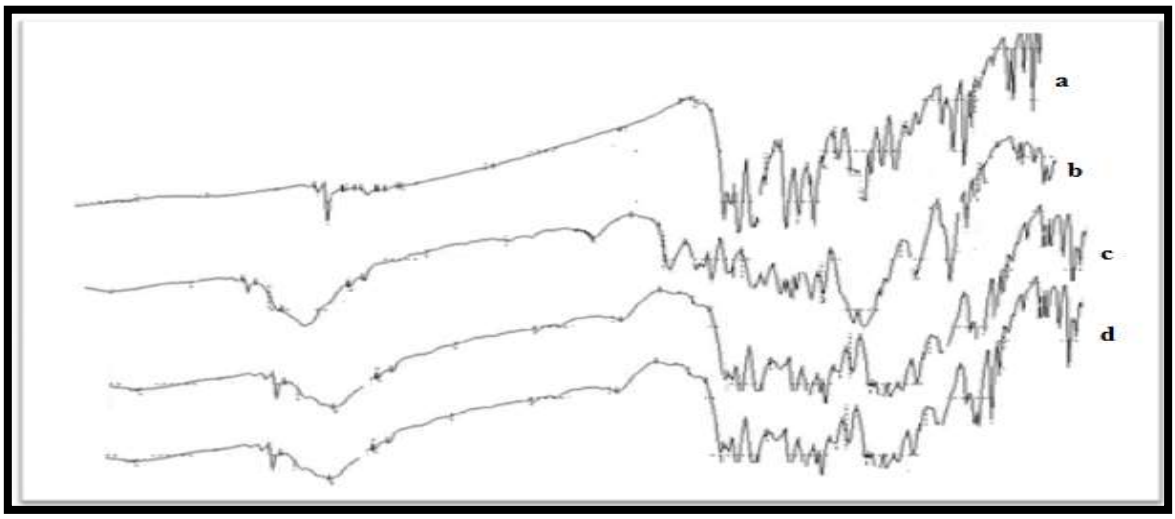


Figure No 6.IR spectra for compatibility study: Lornoxicam (a); Eudragit RS100 (b); Eudragit RS100 (c); Poloxamer 407 (d).



B. DSC Analysis

The Lornoxicam physical state raw as well as in the combination for compatibility studies was determined and no interaction between the Lornoxicam and polymer as well as stabilizer observed. The Drug DSC was mentioned in Figure no 7. The Compatibility of Drug with Polymer was checked by DSC spectra and was shown in figure No 8.

Figure No 7.DSC of Lornoxicam

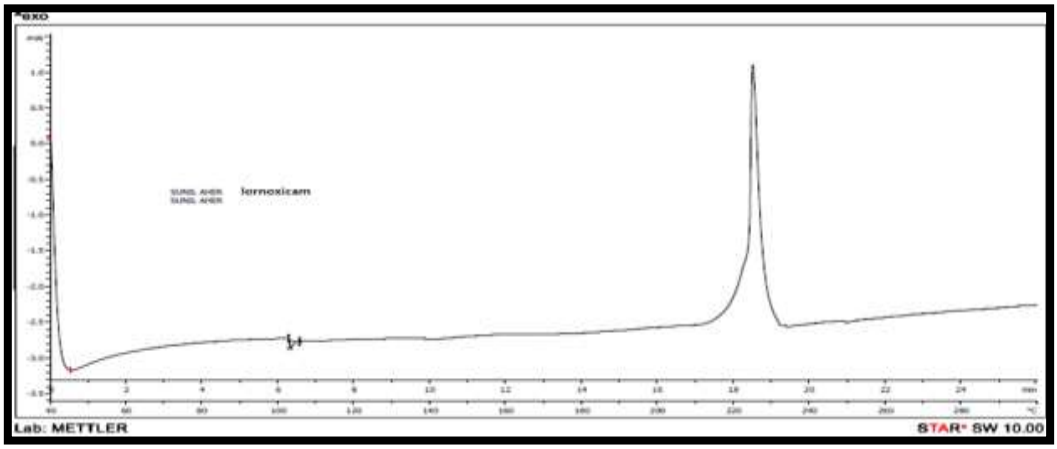
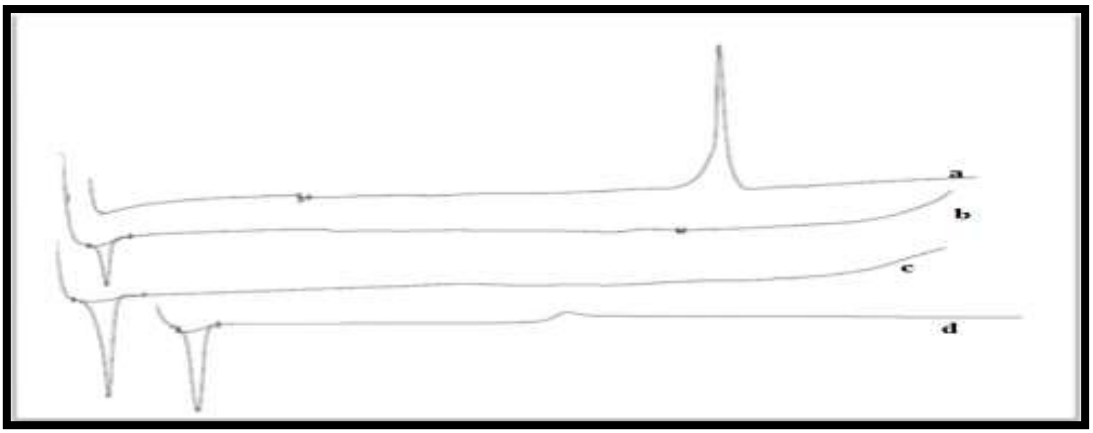


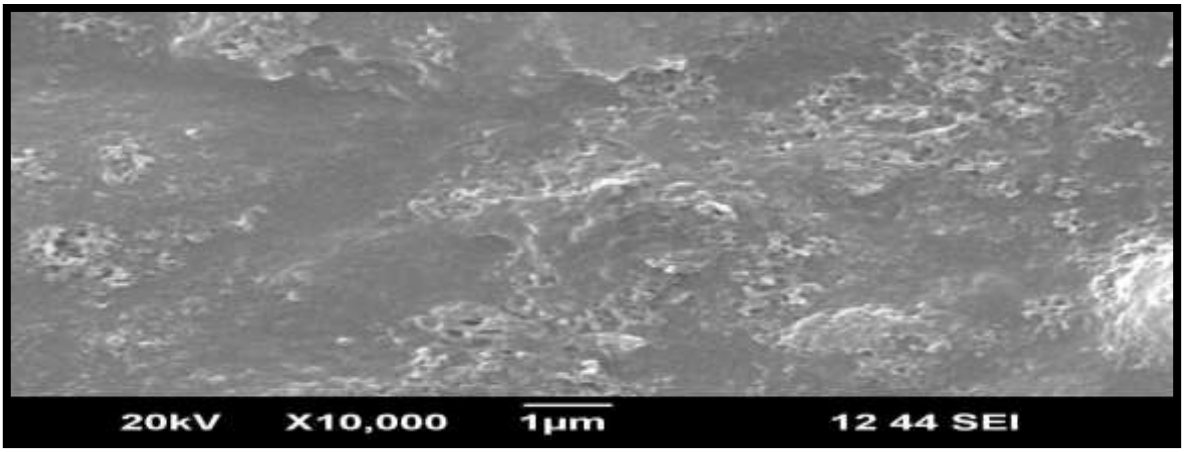
Figure No 8. Compatibility study by DSC: Lornoxicam (a); Eudragit RS100 (b); Eudragit RS100 (c); Poloxamer 407 (d).



C.SEM Scan

The above SEM are of the optimize F4 formulation. On a scale we can clearly see the F4 formulation of Lornoxicam: Eudragit RS100 Particle size 90-100 nm. Were as the formulation F1 to F8Formulation lornoxicam: Eudragit RS100 & EudragitRL100 show particle size in range of 90 nm-480nm.The SEM analysis was mentioned in Figure No 9.

Figure No 9. SEM of optimized F4 formulation.



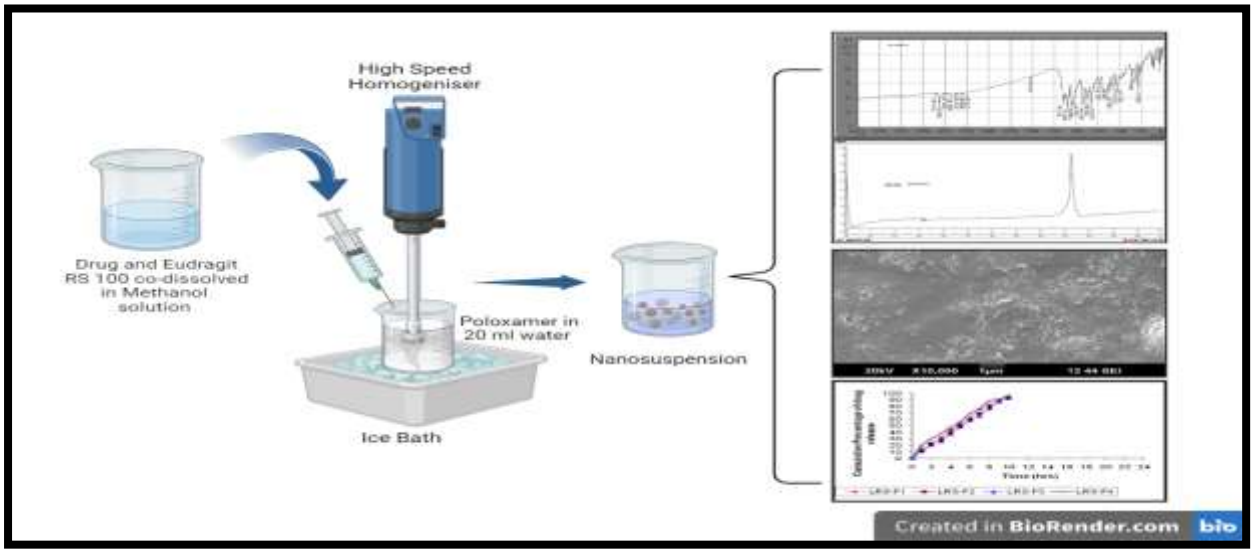
Short term stability studies

Short-term stability Studies were performed for three months for the optimized formulation of Lornoxicam Nanosuspension. The results revealed that the formulation stored at a temperature 4 C showed no change in the in vitro drug release as compared to the release study tested after the formulations 0,1,3 month which means the nanosuspensions are stable at the given temperature. Moreover, the physical appearance of all the nanosuspensions was found to be up to the mark confirming that the nanosuspensions are stable and growth or crystal development was observed. On the other hand, the nanosuspension stored at a temperature 37°C ± 2°C ,65 % RH ± 5 % RH comparatively there is a change in the vitro drug release. The physical appearance of the nanosuspension was found to develop the small crystal growth at this temperature which revealed that the nanosuspension is not stable at this temperature range. So maximum stability is obtained at the temperature 4°C.

4. Conclusion

It is concluded that the polymer Eudragit RS100 with a ratio of drug 1: 2 with the help of stabilizer poloxamer with 1% is effective for formulating the stable nanosuspension for a sustained release of lornoxicam drug with increased dissolution rate lornoxicam nanosuspension can be prepared using Quassi emulsification solvent diffusion method using poloxamer 407 as a stabilizer. Poloxamber 407 is essential to achieve a particle size close to 90-100 nm for optimized formulation were in other formulations the particle size was observed between 90 to 480 nm. The formulations along with Eudragit RS 100 polymer show significant drug release in the dissolution profile of the formulations. Nanosuspension of lornoxicam shows significant drug release determined using phosphate buffer having pH 7.4. The results show the suitability of the method for the preparation of stable nanosuspension of water-insoluble Class II Drugs. As per Research was concluded that the Polymer Eudragit RS100 was best used for the preparation of nanosuspension with the help of Poloxamer 407 as a stabilizer.

Graphical Abstarct:



References:

1. A.T. Serajuddin Salt formation to improve drug solubilityAdv. Drug Deliv. Rev2007
2. Merisko-Liversidge, E.M., Liversidge, G.G, Drug nanoparticles: formulating poorly water-soluble compounds. Toxicol. Pathol. 2008; 36, 43–48
3. Nakach, M., Authelin, J.R., Chamayou, A., Dodds, J, Comparison of various milling technologies for grinding pharmaceutical powders. Inter. J. Mineral. Process. 2004; 74, S173–S181
4. Kavita Joshi,[1] Akhilesh Chandra,[1] , Nanocrystalization: An Emerging Technology to Enhance the Bioavailability of Poorly Soluble Drugs,Pharm Nanotechnol. 2019 Dec; 7(4): 259–278.
5. Jadhav KR,Shaikh IM,Ambade KW, Kadam VJ. Applications of microemulsion based drug delivery system. Cur. Dr. Del.2006; 3(3): 267- 273.
6. Leuner C.Dressman J.Improving drug solubility for oral delivery using solid dispersions. Eur.J. Pharm.Biopharm.2000; 50(1): 47-60
7. Yadav GV, Nanosuspension: A Promising Drug Delivery System, Pharmacophore, 3(5), 2012, 217-243
8. Dubey R. Pure drug nanosuspensions-Impact of nanosuspension technology on drug discovery and development. Drug Del Tech 2006; 6:65-71
9. Bhakay, A., Merwade, M., Bilgili, E., Dave, R.-N., 2011. Novel aspects of wet milling for the production of microsuspensions and nanosuspensions of poorly watersoluble drugs. Drug Dev. Ind. Pharm. 37, 963–976
10. Muller, R.-H., Moschwitzer, J., Bushrab, F.-N., 2006. Manufacturing of nanoparticles by milling and homogenization techniques. Nanopart. Technol. Drug Deliv. 159, 21–51
11. Dr. Sunil J. Aher, Aishwarya S. Patil, Poonam P. Patil, et al. Preparation and characterization of Eudragit based Nanosuspension for oral drug delivery. Eur. Chem. Bull. 2023, 12(Special Issue 5), 6301 – 6310
12. R.H. Mu¨ller, S. Benita, B. Bo¨hm (Eds.), Emulsions and Nanosuspensions for the Formulation of Poorly Soluble Drugs, Medpharm Scientific, Stuttgart, 1998.
13. Dr. Sunil J Aher, Poonam P Patil, et al.Formulation and Evaluation of ketoprofen nanosuspension, European Journal of Molecular & Clinical Medicine, Volume 09, Issue 09, 2022.
14. Sunil J. Aher, Swati Jagdale, Formulation and Evaluation of Zaltoprofen Nanosuspension by Quassi Emulsification Solvent Diffusion Method, WJPR, Volume 4, Issue 2, 979-988, Vol 4, Issue 2, 2015.
15. Rosario, R. Nadia, B. Claudio, M. Francesco, M. Adriana & P. Giovanni., AAPS Pharma scitech., 2006, 7, 27