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FORMULATION AND EVALUATION OF ZALTOPROFEN NANOSUSPENSION BY QUASSI EMULSIFICATION SOLVENT DIFFUSION METHOD

Sunil J. Aher*[1] and Swati Jagdale[2]

[1]Research Scholar, Suresh Gyan Vihar University, mahal Jagatpura, Jaipur.
SRES's, Sanjivani College of Pharmaceutical Education & Research, Kopargaon.
[2]Dept. of Pharmaceutics, MAEER's Maharashtra Institute of Pharmacy, Pune, Dist-Pune, MS, India-411038.

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***Correspondence for Author**
Sunil J. Aher
Research Scholar, Suresh Gyan Vihar University, mahal Jagatpura, Jaipur.

ABSTRACT

Present study was to prepare Zaltoprofen nanosuspension and characterization of the nanosuspension and the aim behind the nanosuspension as it increase the dissolution of the poorly soluble drug belong to the class II example Zaltoprofen was selected and found to increase in invitro dissolution and oral bioavailability of drug .It was prepare by Quassi Emulsification Solvent Diffusion method by using different ratio of drug: polymer: stabilizer .The formulation with a ratio of 1:1:0.5 (drug:polymer:stabilizer)show reduce particle size as well as more dissolution & drug entrapment. The formulations were analyzed for particle size using SEM, Zeta potential determination IR& DSC Studies, *in vitro* drug release studies. The particle size of the formulated nanosuspensions were found in the range of 248-355nm

KEYWORDS: Nanosuspension, Eudragit RL100, Poloxamber407 Zaltoprofen, Quassi emulsification solvent diffusion.

INTRODUCTION

The number of new pharmaceutical compounds with poor aqueous solubility has grown steadily over the last two decades due to the progress in discovery technologies, e.g. high throughput and combinatorial screening tools, during lead development and optimization phases.[1,2] Several of these compounds are mainly categorized as bio pharmaceutics classification system (BCS) class II for which their oral absorption is limited by their

extremely poor solubility in the gastrointestinal tract.[3] Many potential compounds, named candidates, frequently drop out on the way of pharmaceutical development because of their insufficient oral exposure. Therefore, the improvement of solubility and dissolution of poorly water-soluble drugs has become a major field of interest for formulation researchers. Various solubilization technologies have been developed to solve such proposition, so far. These include solid dispersions prepared by spray-drying[4, 5] freeze-drying[6] or hot melt extrusion; complex formation with water-soluble excipients;[7, 8] self-emulsifying drug-delivery systems (SEDDS)[9] and so on. The particle size reduction/milling is also enabling approach for solubilization. By reducing the particle size of the compound, an increase in surface area results in faster dissolution rates according to the Noyes–Whitney equation. However, it is said that reduction of particle size is limited to 23 lm or more, because of the secondary co-aggregation occurring between particles as a result of van der Waals' interaction and electrostatic force.

Quassi emulsification solvent diffusion is a type of top down technologies used for preparation of nanosuspension. It is most advantageous method for preparation of nanosuspension as compared to other method as drugs are water insoluble but polymers are water soluble which make it easy for maintaining the stability of emulsion formed.

Zaltoprofen (ZLT)[10, 11] is a non-steroidal anti-inflammatory drug, and has excellent effects even on post-surgery or post-trauma chronic inflammation. The chemical name of ZLT is (±)-2-(10,11-dihydro- 10-oxodibenzo [*b*,*f*] thiepin-2-yl) propionic acid. ZLT selectively inhibits cyclooxygenase-2 activity and prostaglandin E2 production. It is used in the treatment of rheumatoid arthritis, osteoarthritis, and other chronic inflammatory Pain conditions. ZLT is a unique compound that also has anti-bradykinin activity. It is not only of cyclooxygenases but also of bradykinin-induced 12-lipoxygenase inhibitors.[12]

MATERIALS AND METHODS

2.1. Materials

Zaltoprofen was gifted by ZCL chemicals Ltd. Mumbai, Maharashtra, India. Poloxamber407, Eudragit RL 100 were purchased from Yarrow chemicals Mumbai, Maharashtra and are of AR grade.

2.2 METHODS

Preparation of zaltoprofen nanosuspensions

Zaltoprofen nanosuspensions were prepared by the Quassi emulsification solvent diffusion method. The drug and polymer were co-dissolved in 5 ml of methanol. The solution was to be slowly injected with a syringe containing thin teflon tube into water containing stabilizer poloxamber 407 and it was maintained at low temperature in ice bath protected from sun light. During injection the mixture was stirred well by a high speed homogenizer at 5500 rpm agitation speeds. The solution immediately turned into 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 micro droplets respectively results into the formation of nanosuspension.[13]

EVALUATION OF NANOSUSPENSIONS

Particle Size Analysis

The mean particle size of the nanosuspension was determined by scanning electron microscopy (SEM) Each sample was properly diluted with pro injection water and the reading should be taken at a 90^{o} angle with respect to incident beam.[14]

Amount of Unincorporated Drug

2ml of the freshly prepared nanosuspension was centrifuged at 1100rpm, 10^{o}C for 15min. Then the supernatant was analyzed at 330 nm using U.V spectrophotometer to determine the amount of unincorporated drug.[15,16]

Zeta Potential

Electrophoretic mobility of nanosuspension was obtained by a laser Doppler anemometer. A suitable amount of the sample (50-100µ L) was diluted with 5mL of water (HPLC grade) and placed into the electrophoretic cell of the instrument, where a potential of ±150mV was induced. The ζ -potential value was calculated by the software using smoluchowski's equation.[17]

IN VITRO DRUG RELEASE

In vitro drug release of the nanosuspension was carried out by using USP Dissolution apparatus type2 (paddle type). 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 p^{H} 7.4. Dissolution was carried in

Triplicate for 10 hrs at 37±1^{0}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 analysed at 330 nm using U.V spectrophotometer.

RESULTS AND DISCUSSION

In the present work nanosuspensions of zaltoprofen were formulated using different drug to polymer ratio and with 5500 rpm agitation speeds by quasi emulsion solvent diffusion technique. Particle size was determined for all the 4 formulations by scanning electron microscopy. It was found that the formulations prepared at 5500rpm speed (F5) had smaller particle size of 248 nm were as other formulation found the particle size up to 355 nm. The zeta potential remained in the range of positive values for all batches and varied between + 9.48 mV to 11.45 mV (Table no. 04). The positive surface charge for the nanoparticles was observed due to the presence of the quaternary ammonium groups of Eudragit RL 100. The relative constancy of zeta potential with slight variation indicates that zaltoprofen was encapsulated within the nanoparticles and a major part of drug is not present on the nanoparticle surface. Different drug to polymer ratios had no influence on drug loading efficiency but the formulation with 1:1:0.5 ratio of Zaltoprofen to Eudragit RL100 and Poloxamber407 was found to be effective for production of polymeric nanosuspension stabilizer. The nanosuspension formulation ZRL-F5 had highest drug loading efficiency of 74.13% and the least was for the formulation with 68.88 %. In vitro drug release tests were carried out using dialysis membrane. *In vitro* drug release was carried out for 10 hr and samples were collected at regular time intervals. By comparing the results, the formulations obtained at the end of 10 hrs it was found to be in between 94.81 % with formulation ZRL-F5.

Table no. 01: Formulative variables of zaltoprofen nanosuspensions (F5_F6).

Sr. no	Formulation	Drug (mg)	Polymer (Eudragit RL 100)	Stabilizer % (Poloxamber 407)
01	ZRL-F5	80	80	0.5
02	ZRL-F6	80	160	0.5
03	ZRL-F7	80	80	1
04	ZRL-F8	80	160	1

Table no. 02: Particle size of Zaltoprofen nanosuspensions

Sr. no	Formulation	Particle size (nm)
01	ZRL-F5	248
02	ZRL-F6	300
03	ZRL-F7	350
04	ZRL-F8	355

Table no. 03: Percentage drug unincorporated and entrapped for Zaltoprofen nanosuspensions

Formulation code	% Drug Unincorporated	% Drug Entrapped
ZRL-F5	25.87	74.13
ZRL-F6	27.12	72.88
ZRL-F7	30.77	69.23
ZRL-F8	31.12	68.88

Table no. 04: Zeta potential of Zaltoprofen nanosuspensions

Sr. no.	Formulation	Zeta Potential(mV)
01	ZRLF5	11.45
02	ZRL-F6	10.20
03	ZRL-F7	9.48
04	ZRL-F8	14.26

Table no.05: Percentage cumulative drug release of Zaltoprofen nanosuspensions

Time	F5-ZRL	F6-ZRL	F7-ZRL	F8-ZRL
0	0	0	0	0
1	10.89	11.41	12.11	14.11
2	20.21	24.12	23.43	28.2
3	30.47	32.63	33.41	35.49
4	39.88	39.98	37.98	40.77
5	40.11	41.35	42.84	48.54
6	51.63	53.11	55.11	58.25
7	62.10	63.23	62.43	63.11
8	70.77	74.21	74.28	74.29
9	82.62	81.26	81.45	81.89
10	94.81	96.2	95.26	96.34

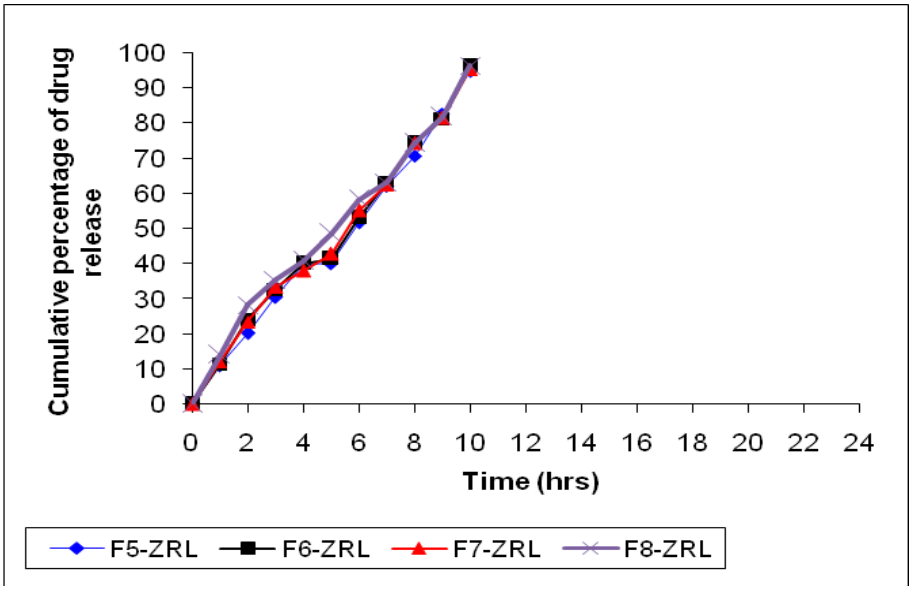

Fig.01: Dissolution profile of nanosuspension (F1-F4)

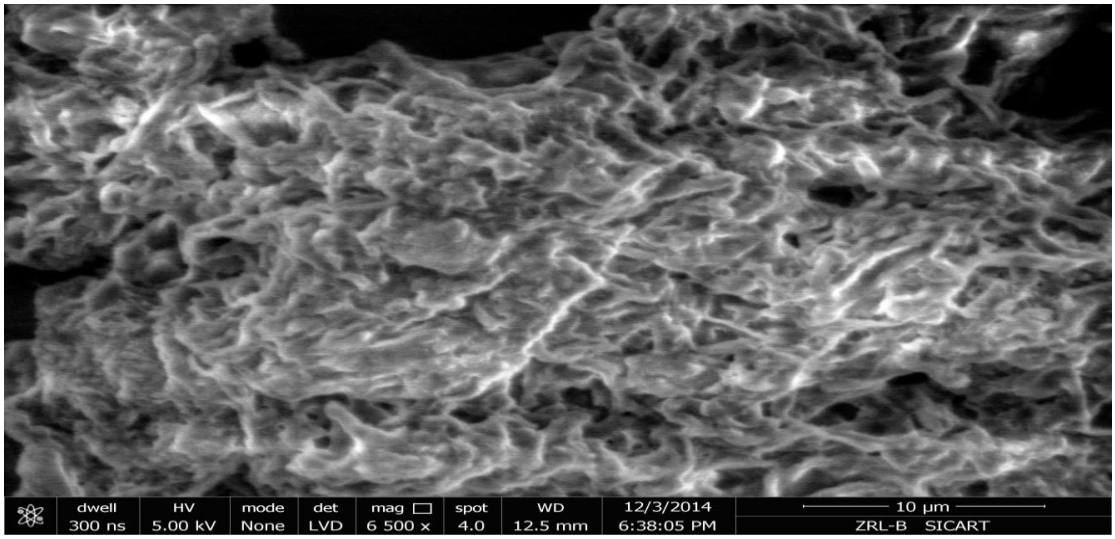

Fig. 02: SEM of formulation F5

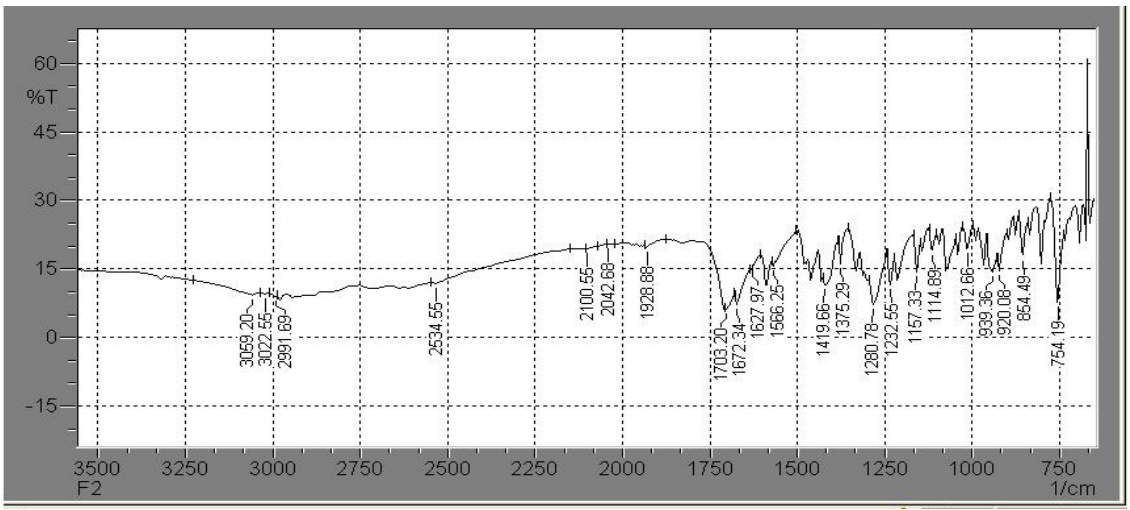

Fig. 03: IR spectrum of Zaltoprofen.

Table no.06: Characteristic frequencies in IR spectrum of Zaltoprofen.

Functional Group	Wave number (cm^{-1})	Standard frequency range
-OH str.	3059.20	3000-3200
Aromatic -C-H- (stretching)	3022.55	3000-34000
Aliphatic –CH str.	2991.63	2800-3000
-C=O str.	1703.20	1680-1880
-C=C- (stretching)	1627.97	1690-1640
-C-O- (stretching)	1012.66	1350-1000
-C-S-C str.	939.36	800-1000

Differential scanning calorimetry (DSC)

DSC study was carried out for drug zaltoprofen. The obtained DSC results are shown in Fig. No. 04. DSC studies indicated the sharp peak at 143.48-147.38°C, which is the melting point of zaltoprofen drug and which indicating the crystal nature of drug.

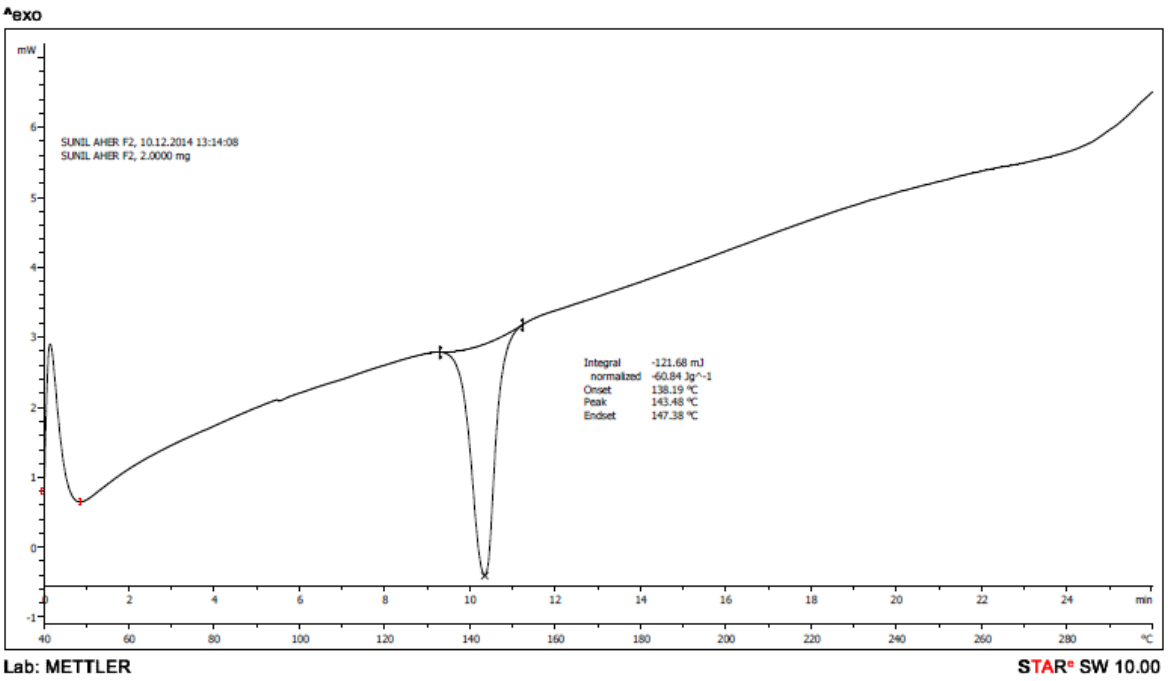

Fig. No.04: DSC of Zaltoprofen.

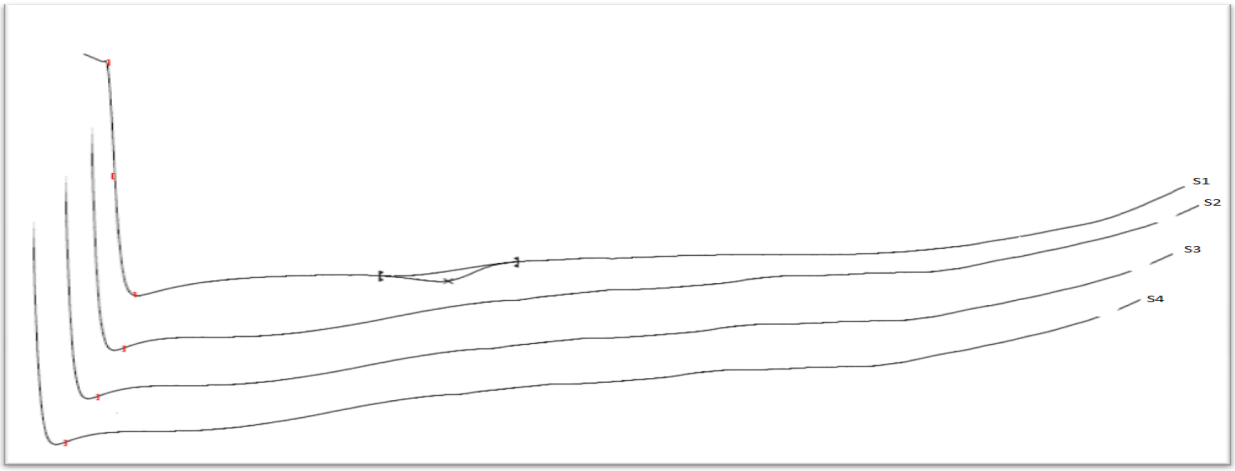

Fig. No. 05: DSC thermographs for compatibility study: Zaltoprofen (S1); Eudragit RL100 (S2); Eudragit RL100 (S3); Poloxamer 407 (S4).

CONCLUSION

It is concluded that the nanosuspension prepare with 1:1:0.5(Eudragit RL100 : Zaltoprofen: Poloxamber407) was found to be best formulation among the nanosuspension which was prepared by using Quassi emulsification solvent diffusion method Poloxamber 407 as a stabilizer is effective at 0.5 % & is essential to achieve a particle size close 248-355 nm. The formulations along with Eudragit RL 100 polymer shows significant drug release shown in dissolution profile of the formulations. Nanosuspension of zaltoprofen shows significant drug release determined using phosphate buffer having pH 7.4. The results show the suitability of method for the preparation of stable nanosuspension of water insoluble drugs.

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CONFLICT OF INTEREST

Authors do not have any conflict of interest.

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