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FORMULATION AND EVALUATION OF SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM OF CEFPODOXIME PROXETIL

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ABSTRACT

Liquid Self micro-emulsifying drug delivery system (L-SMEDDS) was developed with the objective to overcome the problems associated with oral delivery of Cefpodoxime proxetil (CFP), a poorly absorbable, high dose antibiotic having pH dependant solubility. Solubility of CFP in various oils was determined to select the key components of SMEDDS. Various surfactants and co-surfactants were screened for their ability to emulsify the selected oily phase. The optimized L-SMEDDS formulation showed a globule size of 30nm. The optimised SMEDDS formulation showed complete release of CFP within 30 min. Neusilin US2 was used as adsorbing agent to convert optimised L-SMEDDS to Solid Self micro-emulsifying drug delivery system (S-SMEDDS), which were then filled in hard gelatine capsule and evaluated further. The S-SMEDDS showed comparable in vitro dissolution profile as of L-SMEDDS.

KEYWORDS: Cefpodoxime proxetil (CFP), pH dependant solubility, S-SMEDDS.

1. INTRODUCTION

Cefpodoxime proxetil (CFP) is a third generation cephalosporin generally used for the treatment of upper respiratory tract and urinary tract infection. CFP is a prodrug which is hydrolyzed *in-vivo* to its active metabolite Cefpodoxime. The oral bioavailability of CFP in humans is only 50%. The low oral bioavailability of CFP is due to its low water solubility i.e 400µg/ml also due to degradation of its ester side chain by cholinesterases. Lipid based systems are anticipated to protect CFP from degradation by cholinesterase as the cholinesterase cannot hydrolyze triglycerides. SMEDDS is an isotropic mixture of oil, surfactant and co-surfactant which spontaneously forms o/w micro-emulsion on dilution with GI fluids, due to GI motility, thus formulating CFP as SMEDDS can be considered as approach to increase the solubility and bioavailability of CFP. The present study therefore aims to produce a successful design of SMEDDS that can deliver a relatively high dose of CFP in unit dosage form and that can release CFP independent of pH. [1-4)]

2. MATERIALS AND METHODS

2.1 Materials

CEFPODXIME PROXETIL was a generous gift from Lupin Pharmaceuticals Ltd. (Mumbai, India). CAMPUL MCM EP, CAPMUL MCM NF, CAPMUL MCM C8EP, CAPMUL MCM C8 NF were obtained from Abitech corp.(IMCD group Mumbai, India). CREMOPHORE RH40, CREMOPHOPRE EL, SOLUTOL HS15 were obtained from (BASF, Mumbai, India). LABRAFIL M2125CS, LABRAFIL M1944CS were obtained from Gattefosse (Mumbai, India). NEUSILIN US2 was obtained from Fuji Chemicals (Japan). TWEEN 80, TWEEN 20, SPAN 80, SPAN 20, PROPYLENE GLYCOL, were purchased from (Molychem, Mumbai, India).

2.2 Solubility studies

The solubility of drug in various oils was screened. Initially the approximate solubility of drug was found in various oils and latter on solubility was found by UV determination.

a) Approximate solubility

Method: It was measured by weighing 1g oil in a vial and saturation dose of drug was added to it. The saturation dose was then recorded.

b) By UV estimation

Method

An excess amount of CFP was added to 1g of selected vehicle in a vial. The mixture is then cyclomixed for 10 minutes in order to facilitate the proper mixing of CFP in selected vehicle. The mixtures were then shaken for 48 hours in orbital shaker. Mixtures were then centrifuged at 5000 rpm for 5mins. The supernatant was collected and diluted with methanol. Further the amount of CFP dissolved in various vehicles was quantified using UV spectrophotometry.[4,5]

2.3 Emulsification efficiency study

Emulsification efficiency of various surfactants was screened using shake flask method. 300mg of oil and 300mg of surfactant were weighed and mixed together in a vial. The mixture was then cyclomixed for 5 minutes and heated at 45-60ºC for homogenizing the components. From this homogenized mixture 50mg was transferred separately to a beaker and it was diluted to 50ml with Double distilled water to yield micro-emulsion. The solution is then transferred to an iodometric flask and inversions are given if necessary and the number of inversions required to obtain transparent or slight bluish colour solution is noted down, which determines the ease of formation of micro-emulsion. The emulsions were allowed to stand for 2 h and their transmittance was assessed at 638.2 nm by UV-160A double beam spectrophotometer (Shimadzu, Japan) using double distilled water as blank. [6]

2.4 Selection of Co-surfactant

The turbidimetric method was used to assess relative efficacy of the co-surfactant to improve the micro-emulsification ability of the surfactants and also to select best co-surfactant from the large pool of co-surfactants. Oil 300mg, Surfactant 200mg was mixed with 100mg of co-surfactant and the mixture was homogenized with the aid of the gentle heat (45–60 ◦C). 50 mg was accurately weighed and diluted to 50 ml with double distilled water to yield fine emulsion. The ease of formation of emulsions was noted by noting the number of flask inversions required to give uniform emulsion. The resulting emulsions were observed visually for the relative turbidity. The emulsions were allowed to stand for 2 h and their transmittance was measured at 638.2 nm by UV-160A double beam spectrophotometer (Shimadzu, Japan) using double distilled water as blank. As the ratio of co-surfactants to surfactant/s is the same, the turbidity of resulting micro-emulsions will help in assessing the relative efficacy of the co-surfactant to improve the micro-emulsification ability of surfactant/s.[6]

2.5 Formulation of L-SMEDDS

The ratios for oil: surfactant: co-surfactant were selected using shake flask method. 42 different systems of oil: surfactant: co-surfactant were evaluated for the % transmittance value. These 42 systems were constructed by varying oil from 70-30%, surfactant from 30-70% and co-surfactant from 0-30%.

2.6 Optimization of formulae

2.6.1 Freeze thaw cycle

The selected ratios from the 42 systems analyzed were then subjected to alternate freeze thaw cycles. Each ratio was subjected to refrigeration temperature i.e -20ºC for 24 hrs and for the next 24 hrs they were subjected to room temperature. Likewise 3 freeze thaw cycles were carried out and the mixture was observed for any phase separation, drug precipitation or any instability.[6]

2.6.2 Centrifugation

Batches that pass the freeze thaw cycle test are further subjected to centrifugation. The mixture is centrifuged at 4000 rpm for 15minutes and again observed for any signs of phase separations or drug precipitation.[7,8,9]

2.6.3 Robustness to dilution

Robustness of CFP SMEDDS to dilution was studied by diluting it 50, 100 and 1000 times with various dissolution media viz. water, buffer pH 1.2, buffer pH 3.0 and buffer pH 6.8. The diluted nano-emulsions were stored for 12 h and observed for any signs of phase separation or drug precipitation.[10]

2.7 Evaluation of optimized L-SMEDDS

The optimized batch was further evaluated for properties like globule size, zeta potential, polydispersibility index and *in-vitro* dissolution studies.

2.7.1 Globule size, zeta potential, polydispersibility index

The formulation, 50mg was taken and diluted to 50ml with double distilled water and visual observations were done for its emulsification efficiency. Glouble size, zeta potential and polydispersibility index were determined using Horiba zeta-sizer.[10]

2.7.2 *In-vitro* dissolution

The formulated L-SMEDDS were filled into size '00' hard gelatin capsule shell. The *in-vitro* release profile of CFP L-SMEDDS was studied using USP apparatus II (Paddle type) at 37±0.5ºC with a rotating speed of 100 rpm in dissolution media namely, 0.1N HCl and 6.8pH buffer so as to evaluate the effect of pH on *in-vitro* dissolution. During the study 5ml aliqoute was removed at pre-determined interval i.e 5,10,20,30,45,60 from the dissolution medium and replaced with fresh buffer. The amount of CFP released in the dissolution medium was determined by UV spectrophotometer at λmax = 263 nm.[11]

2.8 Conversion of L-SMEDDS to S-SMEDDS

By using Neusilin US2 as an adsorbing agent the optimized L-SMEDDS was converted to free flowing powder.[12]

2.9 Evaluation of S-SMEDDS

The S-SMEDDS formed was then evaluated for micromeritics, SEM, particle size & zeta potential, *in-vitro* dissolution studies.[13]

2.10 Ex-vivo permeability study

Ex-vivo permeability study of S-SMEDDS of CFP was carried out by using non-everted chicken intestinal sacs. Chicken was killed and the duodenal part of small intestine was isolated and washed with distilled water to remove the mucous and lumen content and then placed in cold KRPB (Krebs-Ringer's-Phosphate-buffer, pH 7.2) solution, continuously aerated with the help of electronic aerator. 5-6cm long sacs were prepared by typing up the

two ends of the sac either with cotton or silk thread. 2ml of micro-emulsion of L-SMEDDS formulation of CFP was taken inside the sac. Intestinal sac containing only plain drug solution in KRPB was also included in this study for comparison. The sacs were then taken into different beakers containing 100ml of KRPB solution, continuously bubbled with atmospheric air, maintained at 37±0.5^{o}C and stirred at 100rpm. Aliquots were withdrawn at predetermined interval with a calibrated plastic disposable syringe. Each time an aliquot was withdrawn it was replaced by same quantity of fresh replenished media. The permeability study was carried out for about 60 min. The amount of CFP L-SMEDDS and plain drug permeated across the intestinal sac was determined by measuring the absorbance at 262nm by UV-Visible spectroscopy.[14,15,16,17]

3. RESULTS AND DISCUSSION

3.1 Solubility studies

Solubility studies were aimed at identifying suitable oily phase for the development of CFP SMEDDS. Identifying the suitable oil having maximum solubilising potential is very important to achieve optimum drug loading. Solubility of CFP in various oily phases and buffers is presented in fig 1-2 respectively.

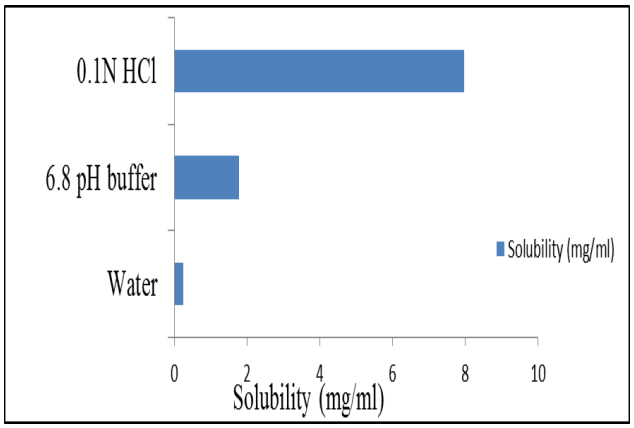

Fig 1. Solubility of CFP in various buffer

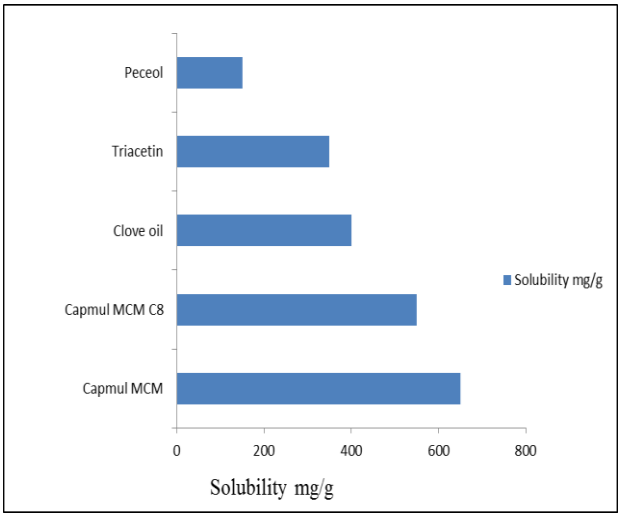

Fig: 2. Solubility of CFP in various oils

Solubility studies clearly indicated that CFP has pH dependant solubility. Among the various oils screened, Capmul MCM (CAP) could solubilise 650 mg of CFP in just 1g oily phase. (Fig 2)

3.2 Screening of surfactant for emulsification efficiency

The % Transmittance values of various dispersions are given in Table I. The ability of various surfactants to emulsify Capmul MCM was checked.

Table 1: List of various surfactants used for screening

Sr. No.	Surfactant	No. of Flask Inversion	% T	Appearance
1	Cremophore EL	8	90.12	Clear
2	Cremophore RH 40	4	96.34	Clear and Bluish
3	Tween 20	14	74.35	Colloidal
4	Tween 80	6	83.46	Turbid
5	Span 20	20	40.90	Turbid
6	Span 80	16	46.59	Turbid
7	Labrasol	20	79.67	Colloidal

The surfactants were compared for their emulsification efficiencies for the selected oily phase i.e. Capmul MCM EP. This study clearly indicated that Cremophore RH40 (Cr.RH40) showed good emulsification efficiency for Capmul MCM followed by Cremophore EL followed by Tween 80 and span 80. From table I it was observed that emulsification efficiency of Cr-RH 40 was excellent compared to other surfactants for CAP, as resultant solution was clear and bluish with %T more than 95%, flask inversions less than 6 inversions. Hence, Cr-RH 40 was selected for CAP and they were subjected to further selection of co-surfactant by spontaneity of emulsification ability.

3.3 Screening of Co-surfactant

Table 2: List of various co-surfactants used for screening

Co-surfactant	Cremophor RH 40		
	No. of Flask	%T	Appearance
Labrafil 2125 CS	1	99.03	Clear and transparent
Labrafil 1944 CS	3	91.01	Clear and Bluish
Propylene glycol	18	81.27	Colloidal
Iso propyl alcohol	16	83.50	Colloidal
Caproyl PGMC	22	60.03	Turbid
Lauroglycol 90	12	24.58	Turbid
PEG 400	5	93.61	Clear and Bluish

It was found that Cremophore RH 40 with Labrafil M 2125 CS (Lab M2125) showed more %T (99.03), with a single flask inversion. Thus Cr.RH40: Lab M 2125 pair was selected to emulsify CAP oil, which showed good spontaneity of emlusion. Thus combination of oil: surfactant: co-surfactant selected was, Campul MCM: Cremophore RH40: Labrafil M2125CS.

3.4 Formulation of L-SMEDDS

From the 42 different systems constructed by varying the concentrations of oil, surfacatant and co-surfactant 4 ratios were selected based on %Transmittance value and no. of flask inversions required.

Table 3: List of ratios selected for further studies

Ingredients (mg)*	Batch No.			
	CLS1	CLS2	CLS3	CLS4
CFP	100	100	100	100
Capmul MCM	153.84	153.84	153.84	153.84
Cr-RH 40	89.74	76.92	83.91	92.30
Lab M 2125	12.82	25.64	41.95	61.53
Total	356.4	356.4	356.4	356.4

3.5 Optimization of formulae

3.5.1 Freeze thaw cycle

The selected four systems were further subjected to freeze thaw cycle. At the end of 3rd cycle the results found were as follows:

Table 4: Results of freeze thaw cycle for selected ratios

Batch no	Evaluation Parameter		Remark
	Phase separation	Drug precipitation	
CLS1	Stable	Clear	Passes
CLS2	Stable	Clear	Passes
CLS3	Stable	Clear	Passes
CLS4	Unstable	Precipitation	Fails

As seen in Table 4 the CLS4 batch was found to be unstable and hence it was eliminated. This batch showed precipitation as well as layer separation hence it was not considered for further studies.

3.5.2 Centrifugation

Table 5: Results of Centrifugation for selected ratios

Batch no	Evaluation Parameter		Remark
	Phase separation	Drug precipitation	
CLS1	Stable	Clear	Passes
CLS2	Stable	Clear	Passes
CLS3	Unstable	Precipitation	Fails

SMEDDS are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and Co-surfactant, with no phase separation, creaming or cracking. Hence centrifugation was carried out on the selected ratios. In the current investigations formulation CLS3 fails the test, while other batches CLS1, CLS2, pass the test and further evaluated for robustness to dilution.

3.5.3 Robustness to dilution

Table 6: Results of Robustness to dilution for CLS1

	Dilution media	Dilution	Evaluation parameters		
			% T	Appearance	Drug precipitation
CLS1	Distilled water	50	94.23	Bluish	No
		100	93.24	Bluish	No
		1000	92.25	Slightly bluish	No

	0.1N HCl (SGF)	50	93.28	Bluish	No
		100	94.23	Bluish	No
		1000	92.45	Slightly bluish	No
	Phosphate buffer pH 6.8 (SIF)	50	93.65	Slightly bluish	No
		100	93.23	Bluish	No
		1000	94.64	Slightly bluish	No

Table 7: Results of Robustness to dilution for CLS2

	Dilution media	Dilution	Evaluation parameters		
			% T	Appearance	Drug precipitation
CLS2	Distilled water	50	99.23	Clear	No
		100	98.56	Bluish	No
		1000	98.25	Clear	No
	0.1N HCl (SGF)	50	99.28	Clear	No
		100	99.54	Clear	No
		1000	98.45	Clear	No
	Phosphate buffer pH 6.8 (SIF)	50	99.65	Bluish	No
		100	99.23	Clear	No
		1000	98.64	Clear	No

It is well known that the addition of surfactants to the micro-emulsion systems causes the interfacial film to stabilize, while the addition of co-surfactant the film expand; thus, the relative proportion of surfactant to co-surfactant has varied effects on the droplet size. Hence to check the stability of the ratios robustness to dilution was carried out. Effect of dilution and pH of dilution media on SMEDDS containing CFP is shown in table 6 and table 7. Batch CLS1 failed the test for robustness to dilution may be as it contains comparatively high concentration of Surfactant as compared to CLS2, and also the %T values of CLS1 is less than 98%. As CLS2 satisfies %T (more than 99%) and dose criteria i.e 5 mg dose /356.4mg in SMEDDS formulation, which is to be filled in hard gelatin capsule hence CLS2 was selected as optimized batch for further evaluation.

3.6 Evaluation of optimized L-SMEDDS

3.6.1 Globule size, Zeta potential and Polydispersibility index

Table 8: Results of globule size, zeta potential and polydispersibility index for selected ratios

Batch No.	Dissolution Media	Parameters	Results
CLS2	Distilled Water	Globule Size (nm) *	33.40
		P.I. *	0.125
		Zeta potential (mV)	-11.5
	0.1 N HCL	Globule Size (nm) *	37.43
		P.I. *	0.126
		Zeta potential (mV)	-10.42
	Phosphate buffer pH 6.8	Globule Size (nm) *	35.02
		P.I. *	0.293
		Zeta potential (mV)	-10.24

* Values are expressed as mean of three replicates

The results indicate that the optimal CFP L-SMEDDS produced a resultant emulsion with a small mean droplet size (30-35nm) and a uniform particle size distribution in both dissolution media (0.1 N HCL and pH 6.8). The surface charge (zeta potential) of the micro-emulsion formed from SMEDDS is believed to play a role in its bioavailability. Because of the presence of fatty acids in the structure of the excipients used, generally the surface charge of the droplet is negative. It was observed the produced SMEDDS has negative Zeta potential (-10 to -11) in both dissolution media (0.1 N HCL and PB pH 6.8). Hence the results obtained for Particle size, PI and ZP were found satisfactory for L-SMEDDS.

3.6.2 In-vitro dissolution study

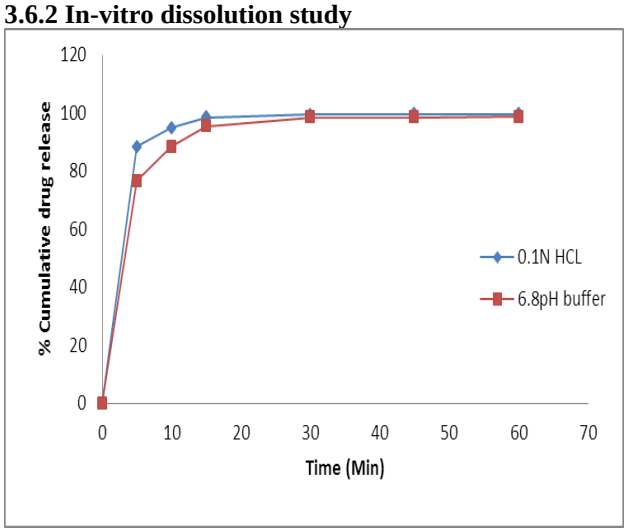

Fig 3: In-vitro dissolution profile of optimized L-SMEDDS

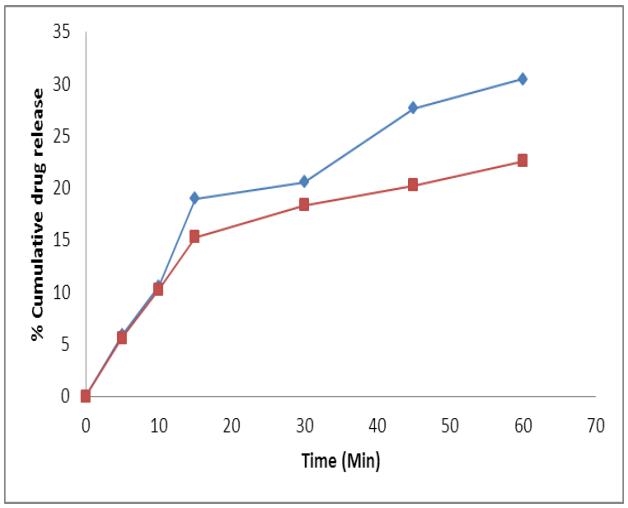

Fig 4: In-vitro dissolution profile of plain CFP

The results of *in vitro* dissolution profiles of optimized CFP L-SMEDDS and pure CFP powder in dissolution media i.e 0.1 N HCL and Phosphate buffer pH 6.8 are given in "Fig 3" and "Fig 4". It was found that Pure CFP release in 0.1 N HCL and Phosphate buffer pH 6.8 was ≤ 30% and ≤ 22% respectively. It is evident from the observation that CFP L-SMEDDS showed a dramatic improvement in the *in vitro* dissolution profile compared to the pure CFP in both dissolution media used. CFP L-SMEDDS showed complete release (≥ 98%) in 30 min in 0.1 N HCL, PB pH 6.8 indicating that the release was not pH dependant for CFP L-SMEDDS.

3.6.3 Drug content

Table 9: Drug content

Batch No.	Drug content (%)*
CLS2	99.24 ± 0.52

* Values are expressed as Mean ± Standard deviation of 3 replicates

3.7 Conversion of L-SMEDDS to S-SMEDDS

Optimization of concentration for adsorbing agent

It was found that 3g of Neusilin US2 could consume about 1.54g of formulation

Therefore,

3g Neusilin US2 ⇨ 1.54 of formulation

X ⇨ 0.356g of formulation

X = 0.23g of Neusilin US2

Neusilin US2 was used as silicate of choice based on previous studies were silicates retained acceptable tabletting properties after incorporation of lipids and surfactants. The Adsorbing capacity of neusilin was determined by taking a fixed amount of neusilin and adding the liquid SMEDDS to it. The amount of Neusilin optimized was found to be 0.23 g.

3.8 Evaluation of optimized S-SMEDDS

3.8.1 Micromeritics

Table 10: Flow properties of S-SMEDDS

Parameter	S-SMEDDS
Angle of Repose* (Degree)	25.73^0 ± 0.04
BD *(gm/ml)	0.26 ± 0.005
TBD* (gm/ml)	0.3421 ± 0.009
Carr's Index *(%)	23.99 ± 0.08
Hausner's Ratio*	1.31

* Values are expressed as mean ± standard deviation of 3 observations

Various micromeritic properties of Cefpodoxime proxetil are shown in table 10. Results showed that the S-SMEDDS has good flow properties.

3.8.2 Particle size, Zeta potential & Polydispersibility index

Table 11: Evaluation of S-SMEDDS

Evaluation Parameter	Results
Particle size * (nm)	33.40
Polydispersibility Index*	0.125
Zeta potential * (mV)	-11.5

*Values are expressed as mean of two replicate

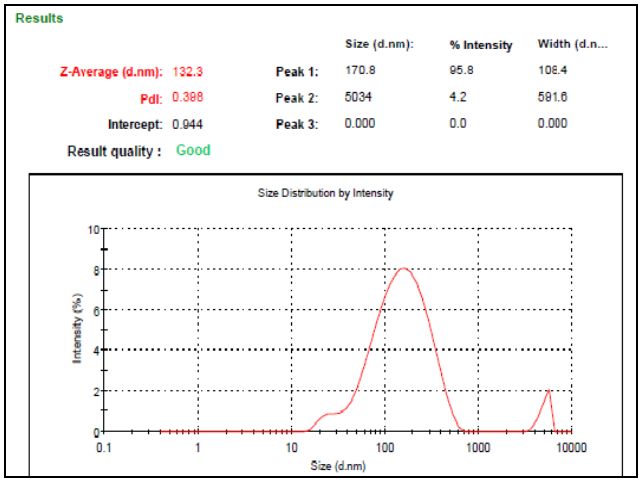

Fig 5: Particle size distribution of optimized S-SMEDDS

The particle size of S-SMEDDS was found to be 132.30 nm with polydispersibility index of 0.398. Since the value of polydispersibility index is less than 1 it indicates uniform distribution of droplets throughout the formulation. Also as zeta potential value is far from 0 it indicates that the formulation is stable.

3.8.3 Scanning Electron Microscopy (SEM)

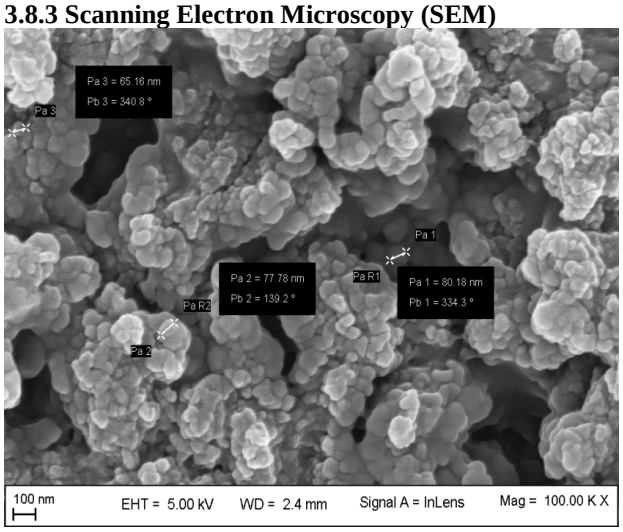

Fig 6: SEM image of CFP loaded S-SMEDDS

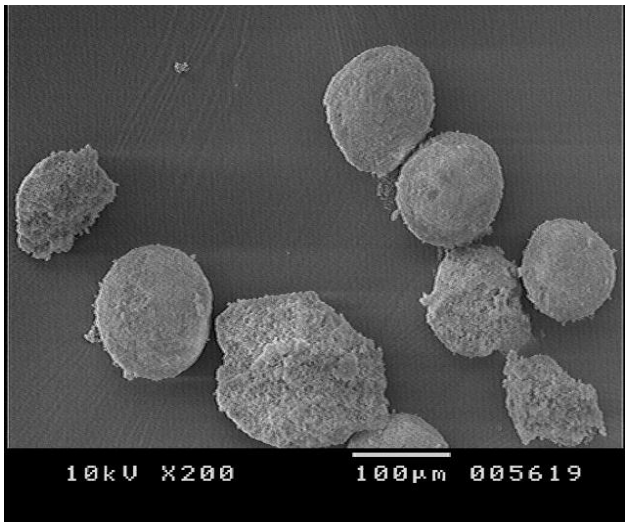

Fig 7: SEM image of Neusilin

From" Fig 6" it is evident that there is loss of crystalline structure of CFP and it has probably been converted to amorphous state i.e completely solubilized in oil phase of L-SMEDDS and adsorbed on Neusilin US2 surface .

3.8.3 Drug content

Table 12: Drug content of optimized S-SMEDDS

Batch No.	Drug content (%)*
CLS2	98.32±0.14

* Values are expressed as Mean ± Standard deviation of three replicates

The value of drug content was obtained well within the range as stated in pharmacopeia

3.8.4 In-vitro dissolution study

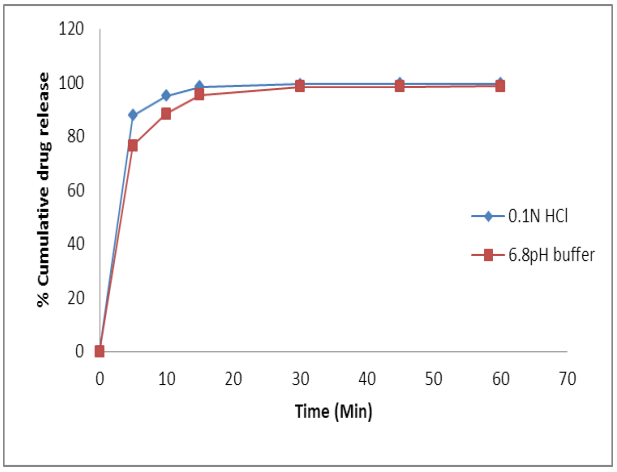

Fig 8: In-vitro dissolution profile of optimized S-SMEDDS

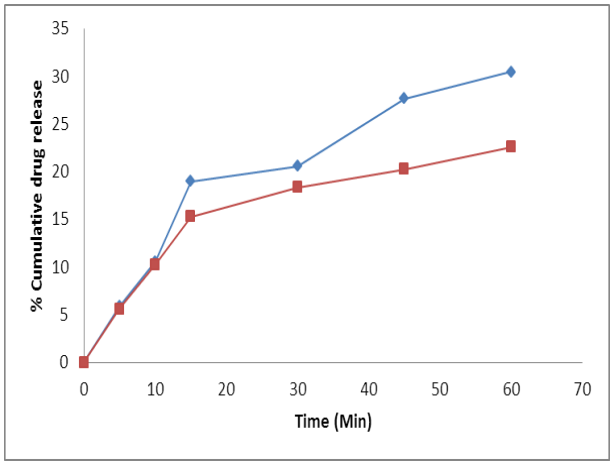

Fig 9: In-vitro dissolution profile of plain CFP

It was found that within 30 mins 99% of the drug was released from the formulation. By comparing the release of formulation and plane drug in buffer pH 6.8 and 0.1 N HCl it is evident that the formulation has served its purpose i.e increase in drug release from formulation as compared to plane drug thus indicates that there is increase in solubility of cefpodoxime proxetil as compared to plane drug. It was found that within 30 mins 99% of the drug was released from the formulation. Also release of drug is independent of pH.

3.8.5 Ex-vivo permeability study

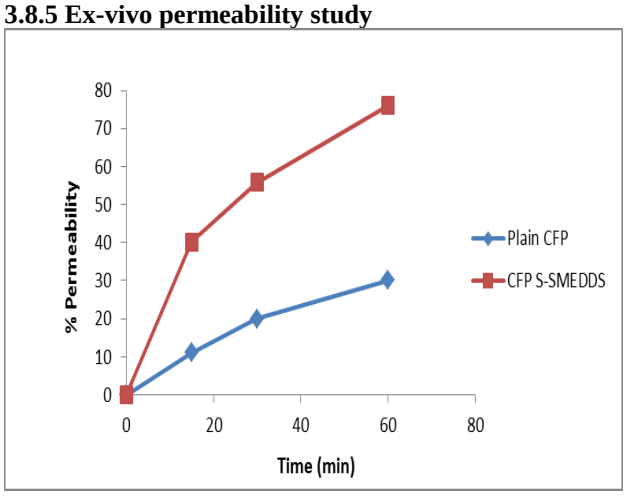

Fig 10: Permeability profile of S-SMEDDS v/s plain drug

Significant increase in permeability of CFP was observed from S-SMEDDS as compared to plain CFP. After 1 hr of study it was observed that, only 30% of CFP was transported through intestinal lumen form CFP solution, on the other hand, 75.98% of CFP was transported through intestinal lumen from micro-emulsion produced form S-SMEDDS formulation. Such a dramatic improvement of permeability of CFP was attributed mainly to the formulation of uniformly dispersed globules with nano size in which CFP is present in dissolved state. These fine globule size increases the surface area and thus facilitates the permeability of drug. Also the presence of bioactive excipients like Cr-RH40 and LM 2125 in the optimized S-SMEDDS formulation may have caused the increase in permeability of CFP as these excipients have been reported to encompass bioactive role in transportation of drugs through intestinal wall.

5. CONCLUSION

Solid Self Micro-emulsifying formulation of Cefpodoxime proxetil containing Capmul MCM EP as oily phase, Cremophore RH40 as surfactant and Labrafil M2125 as co-surfactant was prepared. An improvement in in-vitro dissolution profile was evident due to presence of CFP in solubilised form in oil micro-droplets. A significant increase in permeability of CFP SMEDDS was evident as compared to plain CFP. Conversion of CFP loaded Liquid SMEDDS to Solid SMEDDS also serve to overcome the traditional drawbacks of Liquid SMEDDS.

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