JNROnline Journal
ISSN:2320-3358
ISSN:0972-5547

Journal of Natural Remedies
Vol. 22, No. 1(1), (2021)

UTILIZATION OF SOLUPLUS FOR THE PREPARATION OF ORAL LIQUID SUPERSATURABLE SELF-EMULSIFYING DRUG DELIVERY SYSTEM OF CILOSTAZOL

Ali N. Wannas[*], *Nidhal K. Maraie*[2], *Mayssam H. Mohammed Ali*[3], *Aseel S. Najim*[4]

[*]Department of pharmaceutics, faculty of pharmacy, university of Kufa, Al-Najaf, Iraq.

[2] Department of pharmaceutics, Collage of pharmacy, Mustansiriyah University, Baghdad, Iraq.

[3]Al Rasheed university college, pharmacy department, Baghdad, Iraq.

[4]Ashur university college, pharmacy department, Baghdad, Iraq.

ABSTRACT:

Objective: This study aimed to prepare soluplus based liquid supersaturable self-emulsifying drug delivery system (S-SEDD) of cilostazol for oral use.

Method: The best liquid self-emulsifying drug delivery (liquid SEDD) formula previously prepared in our laboratory containing oleic acid (10%) as oil, tween 80 (45%) as surfactant and transcutol (45%) as co-surfactant (100 µl, 450 µl and 450 µl respectively) was found to consist of high percentage of vehicles (oil, surfactant and co-surfactant) that might be irritant upon oral administration, therefore, this formula was changed into liquid supersaturable self-emulsifying drug delivery system (S-SEDD) using different percent of soluplus as precipitation inhibitor as well as reducing the vehicle content to the minimum required amount and keeping the same dug content (50 mg). The efficiency of soluplus (as precipitation inhibitor) was evaluated by precipitation test using in-vitro dissolution study under non-sink conditions (in 200 ml dissolution medium pH 1.2 for 2 hours and pH 6.8 for 1 hour) in comparison to the liquid SEDD previously prepared in our laboratory. The droplet size of supersaturated emulsion was measured, in addition to characterization of the precipitate by measuring its melting point, IR and DSC spectrum.

Result: The result showed that the formula (LS-3) containing 5% w/w soluplus in addition to oleic acid 25 µl(10%), tween 80 112.5 µl (45%) and transcutol 112.5µl (45%) was effectively retarded drug precipitation and maintained>90% of cilostazol in the solubilized form after 3 hours in non- sink conditions similar to the previously prepared liquid SEDD although it contains one forth the volume of content. The droplet size of the supersaturated SEDD was <250 nm.

Conclusion: This study succeeded to prepare cilostazol liquid oral dosage form using supersaturated self-emulsification technology utilizing soluplus with minimum vehicle ingredients in comparison to liquid SEDD that improve drug solubility, absorption and reducing bioavailability variation with no vehicle-related side effects that will lead to improving patient compliance.

Keywords:liquid supersaturable self-emulsifying drug delivery system (S-SEDD), cilostazol, solubility, oleic acid, soluplus,

INTRODUCTION:

Cilostazol is cyclic AMP (cAMP) phosphodiesterase III inhibitors (class II), inhibiting phosphodiesterase activity and so suppressing cAMP degradation with a resultant increase in (cAMP) in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation, respectively.Its absorption from the gastrointestinal tract is slow, incomplete, and variable[(1)].

Self-emulsifying drug delivery (SEDD) is one of the pharmaceutical technologies that has been used to enhance drug dissolution and/or absorption.It is a pre-concentrate oil, cosurfactant and surfactant mixture that utilizes the concept of in-situ emulsion formation upon water dilution in the gastrointestinal tract which depends on the ease of water penetration into a gel, crystalline or liquid formed on the exterior surface of droplets; however the large quantities of the vehicle need to deliver could cause sever GIT side effects after long term administration [(2, 3)].

The supersaturable self-emulsifying drug delivery system(S-SEDD) is designed to generate a protected supersaturated drug state after dissolution from suitable dosage form into an aqueous

dissolution media by utilizing precipitation inhibitor with minimum vehicle ingredients in comparison to liquid SEDD. The supersaturation will increase the thermodynamic activity of drug beyond the limit of its solubility resulting in an increase in the driving force to transit into and across the biological membranes. The S-SEDD usually contains a reduced level of precipitation inhibitor polymers (soluplus) to prevent precipitation of drug in its supersaturated state and a small quantity of surfactant can stabilize the drug in the supersaturated state [(4)].

soluplus is a graft copolymer consisting of polyvinyl caprolactam (57%), polyvinyl acetate (30%), and polyethylene glycol (PEG 6000)(13%). It is an amphiphilic polymeric solubilizer) with bi-functional structural characters, so it can act as a matrix polymer for solid solutions, and it is capable of solubilizing poorly soluble drugs producing a protected supersaturable state with a higher concentration-time profile compared to conventional SEDD in aqueous media[(5)].

The aim of this work is to utilize soluplus to prepare oral dosage form containing supersaturable spontaneous self-emulsifying delivery system for cilostazol that may improve drug absorption and bioavailability leading to reduce dose size and drug –excipient side effects that may improve patient compliance.

MATERIAL AND METHOD:

MATERIALS:

Cilostazol was supplied from Hangzhou Hyper chemicals (China), oleic acid, was obtained from G.C.C., (UK), soluplus were obtained from BASF, Switzerland, transcutol was obtained from GattefosseCorporation (USA) and Tween 80 were supplied from CDH (India).

METHOD:

Preparation of liquid supersaturable self-emulsifying formulas (S-SEDD) of cilostazol

The best formula of liquid SEDD (LT1) from our previous study[(6)] was selected to be converted into liquid supersaturable formulas (S-SEDD) by using precipitation inhibitor (soluplus). LT1 containing 0.1 ml oleic acid (10%), 0.45 ml tween 80 (45%) and 0.45ml transcutol (45%).

The method of preparation involved mixing soluplus (in different amount 1%, 2.5%, 5%, 7.5%, 10% and 20%) with cilostazol (50mg) in a mortar for 5 minutes, then this mixture was added to homogenous mixture of oleic acid:tween 80:transcutol (2.5%:12.5%:12.5%, which is one forth the contents of LT1 SEDD formula) and vortexed at 40°C until a transparent liquid was obtained[(7)]. Seven liquid supersaturable formulas (S-SEDD) were prepared as shown in table (1).

Table 1: Liquid supersaturable prepared formulas (S-SEDD) for cilostazol

Liquid supersaturable Formula	Soluplus w/w%
LS1	-
LS2	1%
LS3	2.5%
LS4	5%
LS5	7.5%
LS6	10%
LS7	20%

In vitro dissolution study for liquid supersaturable formulas (S-SEDD) (precipitation test)

Cilostazol liquid supersaturable formulas (LS1 – LS7) formulations were filled in a hard gelatin capsule size 0 and placed in 200 mL of 0.1N HCl in a dissolution vessel of USP dissolution apparatus II (Paddle) for two hours, and then tribasic sodium phosphatewas added to make the pH 6.8. The temperature was kept at 37°C, and the rotation rate was kept at 75 rpm. Three ml samples were withdrawn from the test medium without volume replenishment at (5, 10, 15, 30, 60, 30, 45, 60)min, 2 hours, 3hours, 4 hours, 5 hours, and 6 hours. Withdrawn samples were filtered through a 0.45 µm filter medium and then analyzed using UV-spectrophotometer for measuring their UV absorbance at 257 nm [(8, 9)].

Droplet size distribution and polydispersity index measurementof supersaturated emulsion duringprecipitation test

Droplet size distribution and polydispersity index (PDI) measurements were performed for emulsion of liquid S-SEDD formulations (LS1 and LS4) by using particle size analyzer ABT-9000 nanolaser. The lower value of (PDI) the better uniformity of droplet size within the formulation[10].

Characterization of cilostazol precipitate

The precipitate that formed during in-vitro dissolution study for liquid supersaturable formulas (S-SEDD) (precipitation test)was separated from dissolution media by centrifugation and then dried for characterized.

Melting point determination

The melting point of precipitate was measured using a capillary tube method according to the USP. The glass tube is sealed from one side and dipped in a small quantity of cilostazol powder then positioned inside the electrical (Stuart) melting point apparatus, and complete drug powder melting was reached after gradually increasing the temperature [11].

Differential scanning calorimetry (DSC)

The DSC technique was performed for the pure drug (cilostazol) and the precipitate. The procedure includes putting the solid sample in tight aluminum pans and the temperature was elevated at the rate of 20°C/min with a temperature range of 40°C to 250°C in DSC instrument[12, 13].

FTIR spectroscopy

A sample (4mg) of pure cilostazol powder and precipitate, each one separately was mixed with dry potassium bromide and pressed in the form of a disc. The disc was analyzed by FTIR spectroscopy (at a range of 4000 cm^{-1} to 400 cm^{-1})[14].

RESULTS AND DISCUSION:

In vitro dissolution study for liquid supersaturable formulas (S-SEDD) (precipitation test)

The ability of soluplus to inhibit cilostazol precipitation from selected SEDD formula (LT1) was evaluated under non-sink conditions 0.1N pH 1.2 for two hours and pH 6.8 for another 4 hours to simulate normal physiologic pH change in GIT. The release was determined for selected (Lt1) and the prepared supersaturable liquid formulas (LS1-LS7) that contain one-fourth of the vehicle (oil, surfactant, and co-surfactant) and different amounts of soluplus as shown in figure (1and 2).

The release profile of cilostazol from liquid S-SEDD formulations (LS1-LS7) are shown initial quick release (initial peak release) with in the first 15 min indication rapid formation of the self-nanoemulsion upon contact with the dissolution medium [7], and continued for 6 hours. Upon comparing the drug release from LT1 (the selected liquid SEDD formula, not containing soluplus) to LS1 (not containing soluplus but containing ¼ amount of oil, surfactant and co-surfactant of LT1 formula), it was found that both formulas gave initial peak release within 15 min but the release of LT1 continued for 6 hours while for LS1 formula there was significant ($p<0.05$) decline in drug release after 15 min (figure 3.14) due to rapid precipitation of the drug, while LS2-LS4 containing increasing amount of soluplus 1%, 2.5% and 5% respectively, the drug release continued for 6 hours indicating decrease in cilostazol precipitation (in comparison to LS1) with the increase of soluplus concentration with no significant differences ($p<0.05$) since the polycaprolactam moiety of soluplus (hydrophobic compartment of the amphiphilic polymer) would be incorporated and/or adsorbed into cilostazol loaded droplets forming a condensed structure and also polyethylene glycol (the hydrophilic group) would provide a sterically stabilization after dilution[5].As the concentration of soluplus increased above 5% as in LS5, LS6, and LS7 the rate and extent of cilostazol release decrease due to the amount of soluplus exceed the critical level where the polymer aggregates to form its own micelle structure instead of being incorporated into droplets or stabilizing emulsions, and so the soluplus loose packing of

interfacial layers leading to destabilizing cilostazol-loaded emulsion [15, 16].
LS4 was selected as the optimum cilostazol liquid supersaturable SEDD formula since it showed no significant difference ($p>0.05$) in rate and extent of drug release from LT1 (selected liquid SEDD formula) although it contains ¼ amount of oil, surfactant and co-surfactant available in LT1 formula with the same amount of drug and same volume indicating that the drug in LS4 formula reached supersaturation without precipitation with initial quick release with 15 min (97%) and continued for 6 hours as shown in figure (3).

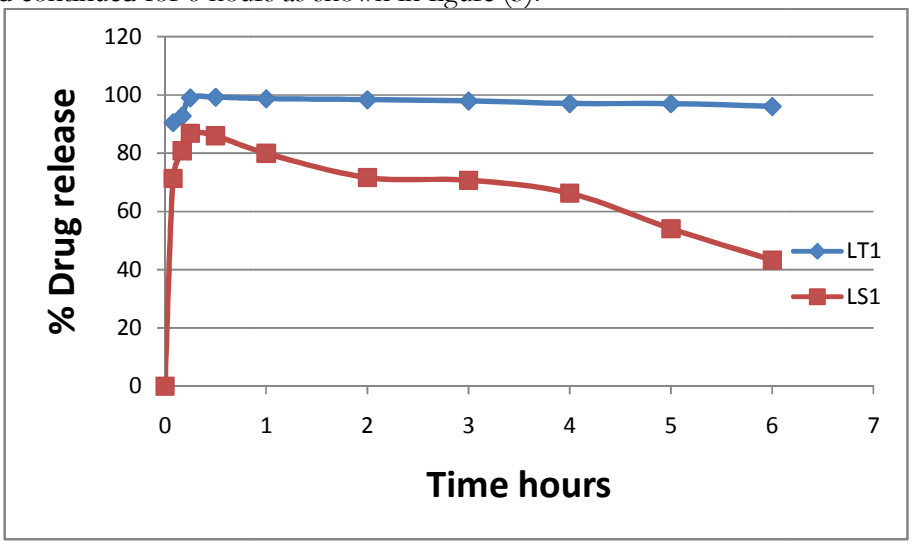


Fig.1: In-vitro release of cilostazol from LT1 and LS1 formulas (n=3) in pH 1.2 for the first 2 hours followed in pH 6.8 at 37˚C.

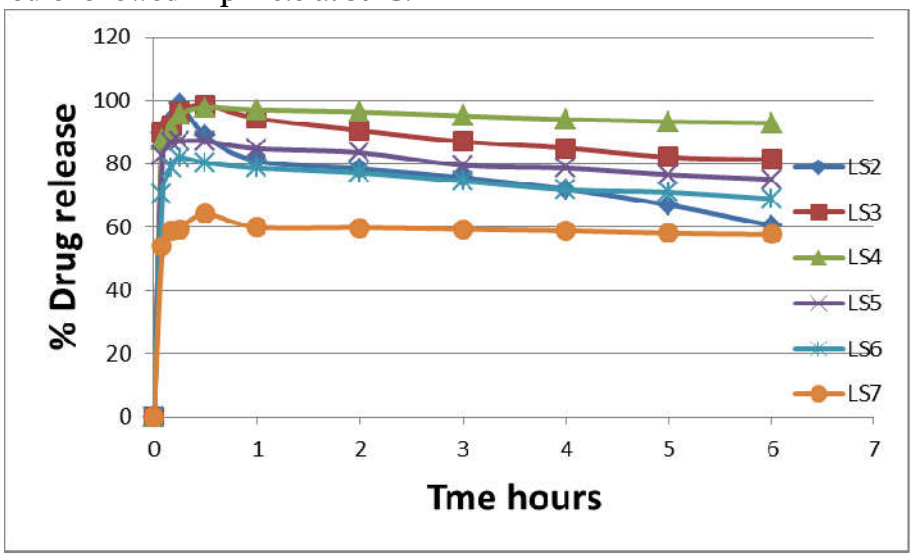


Fig.2:In-vitro release of cilostazol from LS2- LS7 formulas (n=3) in pH 1.2 for the first 2 hours followed in pH 6.8 at 37˚C.

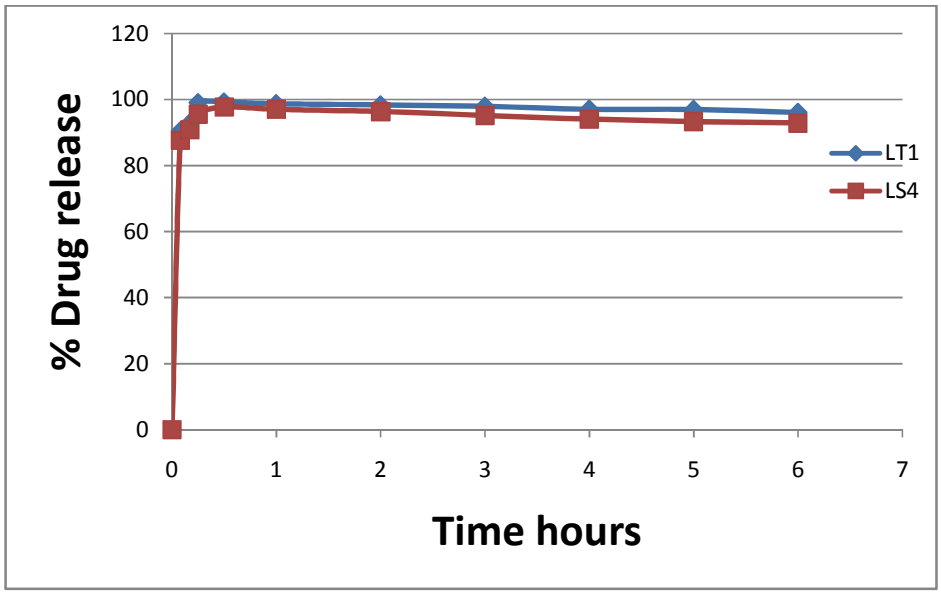


Fig.3:In-vitro release of cilostazol from LS4 and LT1 formulas (n=3) in pH 1.2 for the first 2 hours, followed in pH 6.8 at 37˚C.

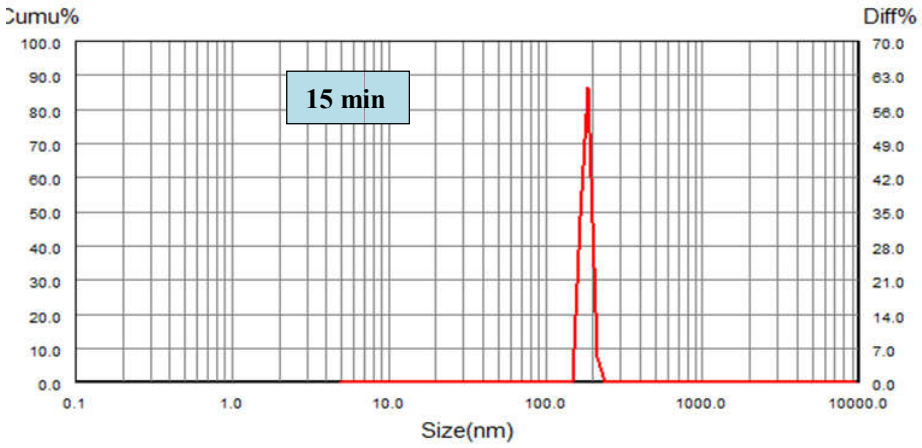
Droplet size distribution and polydispersity index measurement of supersaturated emulsion during precipitation test

The produced emulsion the selected of liquid S-SEDD formulations (LS1 and LS4) was characterized by measurement of the droplet size and polydispersity during precipitation test at (15, 30, 60, 30, 45, 60)min, 2 hours, 3hours, 4 hours, 5 hours, and 6 hours. As shown in table (2) and figure (4 and 5).

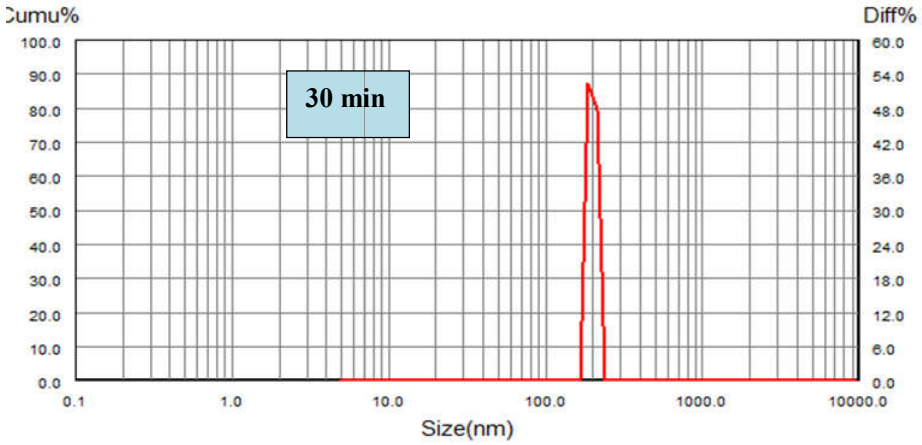
During the test period (6 hours) it was found that the droplet size of the LS4 emulsion was less than 250 nm while that of LS1 was larger than 10 µm and this is related to the presence of soluplus in suitable amount that can effectively prevent drug precipitation[17].

Table 2:Droplet size distribution and polydispersity index measurement (PDI) for the S-SEDD formulas (LS1 and LS4)

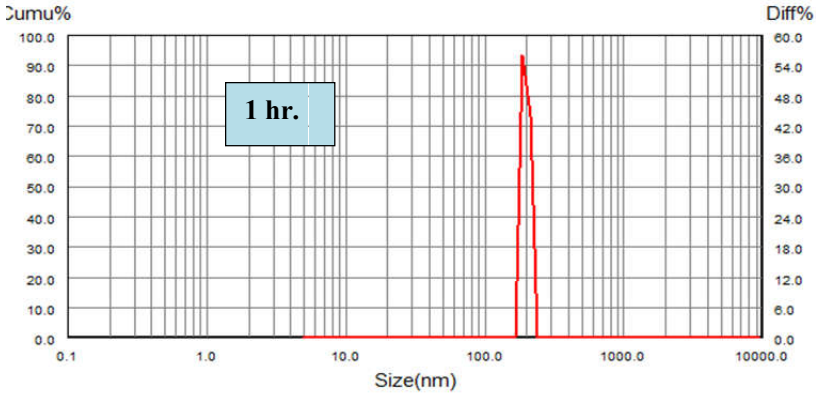
LS4	Droplet size nm	PDI	LS1	Droplet size	PDI
15 min	182	0.012	15 min	235	0.012
30 min	197	0.009	30 min	345	0.007
1 hr.	198	0.009	1 hr.	450	0.026
2 hr.	200	0.009	2 hr.	950	0.014
3 hr.	202	0.012	3 hr.	1550	0.014
4 hr.	205	0.011	4 hr.	2820	0.010
5 hr.	210	0.012	5 hr.	4700	0.016
6 hr.	250	0.010	6 hr.	<10000	



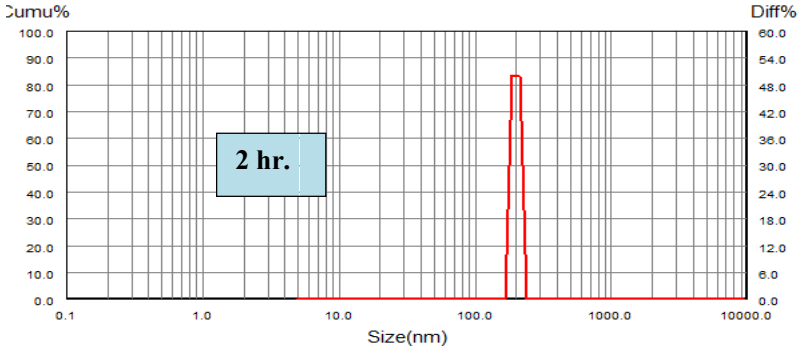
Diam nm	Percent
158	0.00
164	10.74
170	21.48
177	34.01
184	53.31
191	72.61
198	91.91
206	96.22
214	98.00
223	100.00



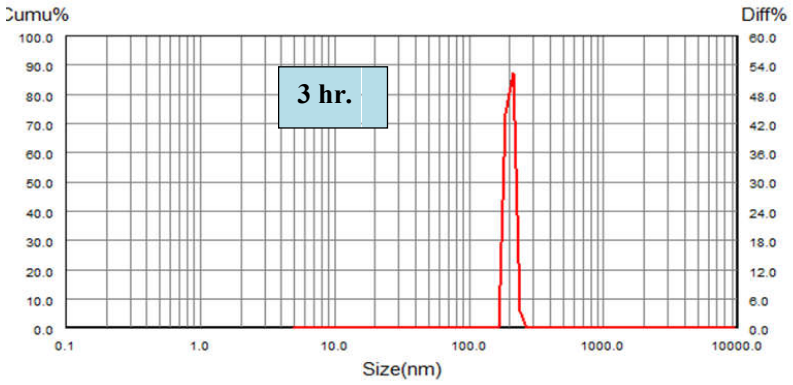
Diam nm	Percent
177	0.00
181	9.51
186	21.40
191	33.29
196	45.17
201	56.28
206	66.22
211	76.15
217	88.07
223	100.00



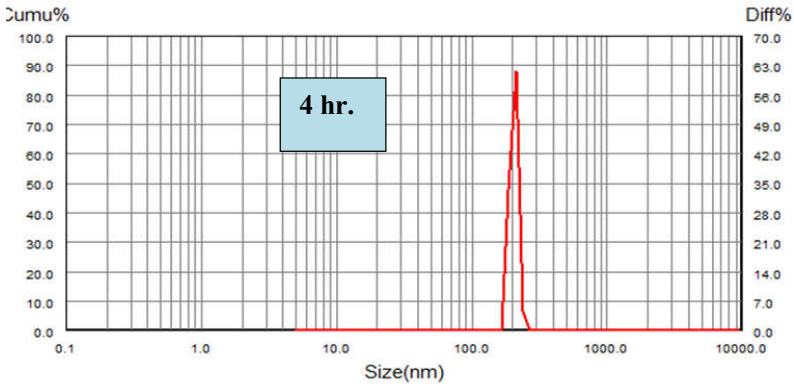
Diam nm	Percent
177	0.00
181	10.18
186	22.92
191	35.65
196	48.38
201	59.69
206	68.85
211	78.01
217	89.00
223	100.00



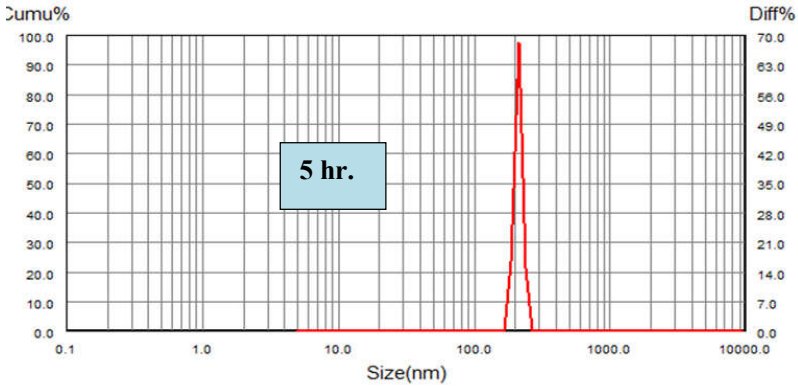
Diam nm	Percent
177	0.00
181	9.12
186	20.53
191	31.94
196	43.35
201	54.34
206	64.72
211	75.09
217	87.54
223	100.00



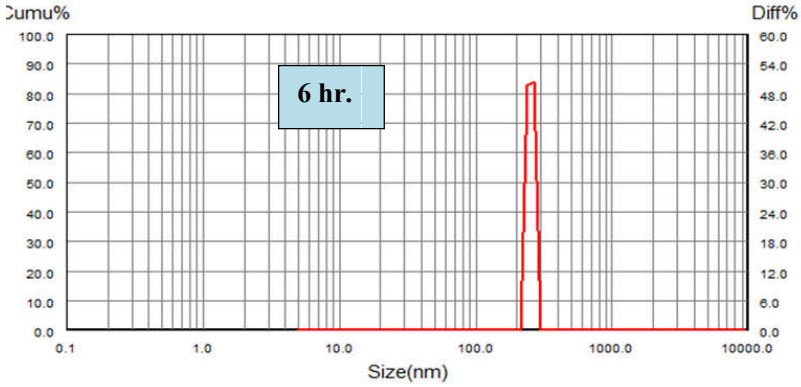
Diam nm	Percent
177	0.00
183	12.01
191	28.03
198	42.05
206	59.34
214	76.81
222	94.28
231	97.51
240	98.69
250	100.00



Diam nm	Percent
177	0.00
183	9.14
191	21.34
198	32.01
206	51.54
214	72.13
222	92.72
231	96.68
240	98.25
250	100.00

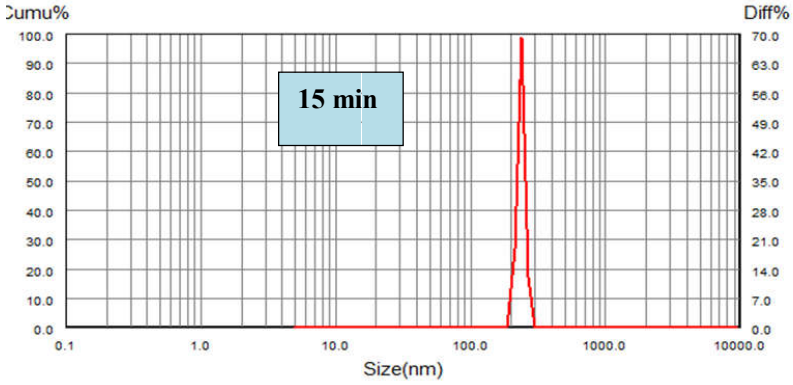


Diam nm	Percent
177	0.00
183	4.52
191	10.56
198	15.85
206	36.52
214	59.29
222	82.06
231	89.38
240	94.41
250	100.00

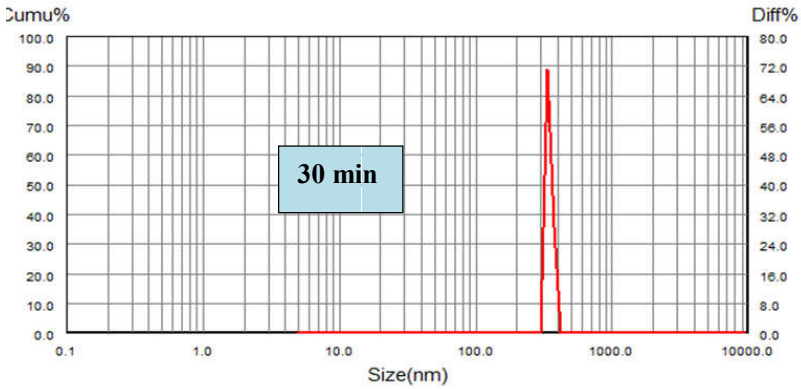


Diam nm	Percent
223	0.00
228	9.20
234	20.24
240	31.28
247	44.16
253	54.55
260	65.91
266	75.65
273	87.01
281	100.00

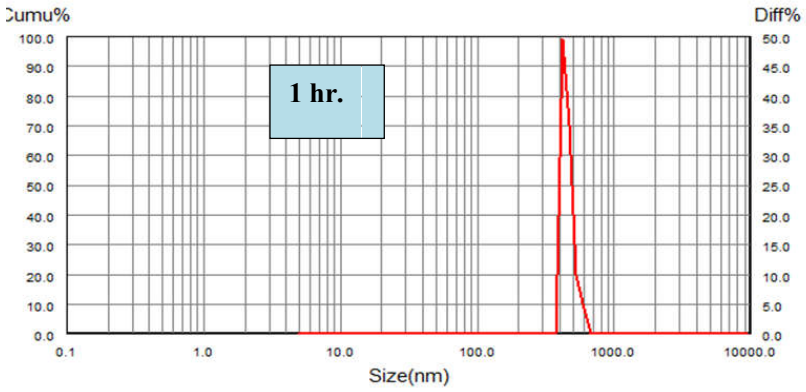
Fig.4: Droplet size distribution of the LS4 during precipitation test at (15, 30, 60, 30, 45, 60)min, 2 hours, 3hours, 4 hours, 5 hours, and 6 hours.



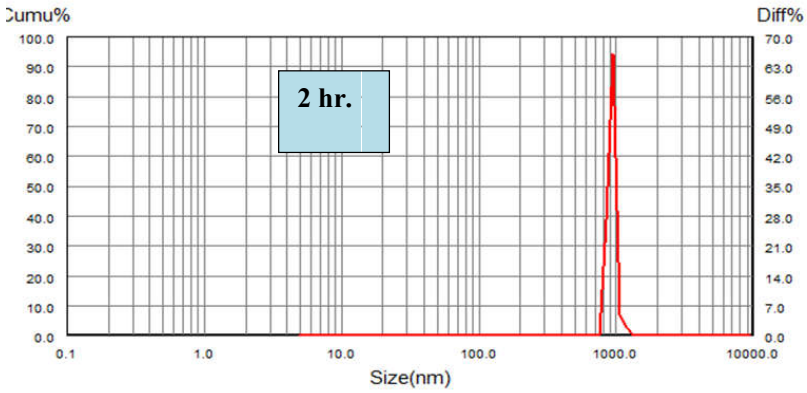
Diam nm	Percent
199	0.00
206	5.50
214	11.80
223	18.88
231	39.34
241	64.91
250	87.93
260	91.82
270	95.71
281	100.00



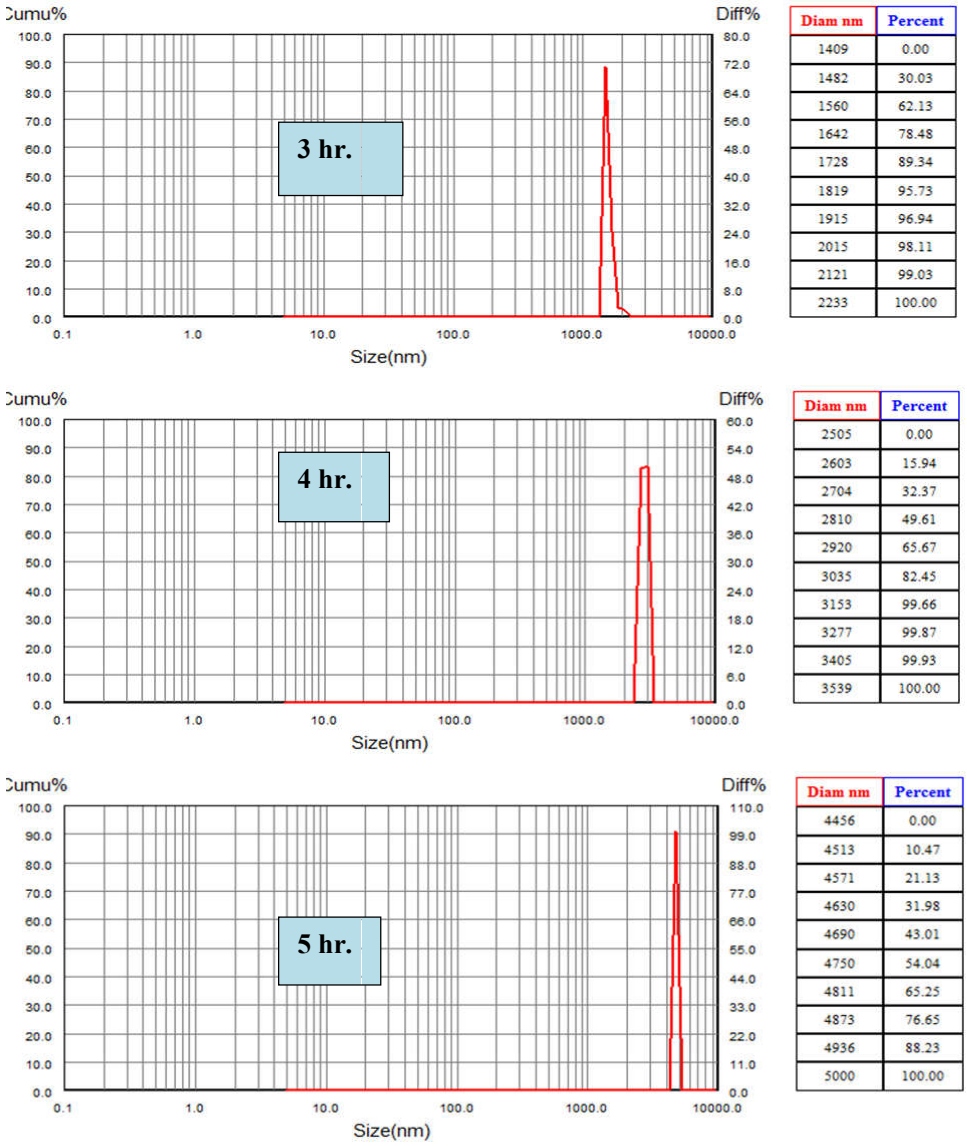
Diam nm	Percent
315	0.00
323	14.97
331	29.94
340	46.78
349	63.63
358	74.39
367	80.30
377	86.87
386	92.77
397	100.00



Diam nm	Percent
397	0.00
417	20.64
439	43.35
462	60.45
487	76.49
512	86.79
539	91.19
567	95.24
597	97.54
629	100.00



Diam nm	Percent
792	0.00
833	11.50
877	23.84
923	47.95
971	77.22
1022	94.09
1076	96.27
1132	98.19
1192	99.07
1255	100.00



Diam nm	Percent
1409	0.00
1482	30.03
1560	62.13
1642	78.48
1728	89.34
1819	95.73
1915	96.94
2015	98.11
2121	99.03
2233	100.00

Diam nm	Percent
2505	0.00
2603	15.94
2704	32.37
2810	49.61
2920	65.67
3035	82.45
3153	99.66
3277	99.87
3405	99.93
3539	100.00

Diam nm	Percent
4456	0.00
4513	10.47
4571	21.13
4630	31.98
4690	43.01
4750	54.04
4811	65.25
4873	76.65
4936	88.23
5000	100.00

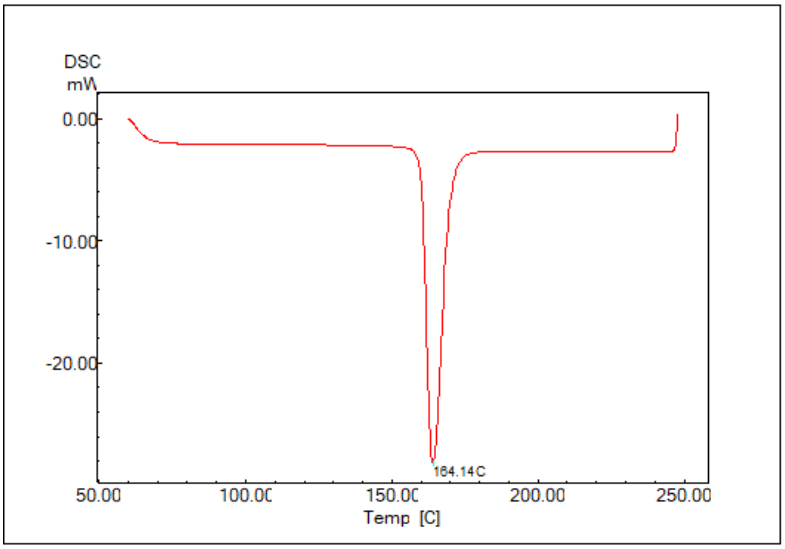
Fig.5: Droplet size distribution of the LS1 during precipitation test at (15, 30, 60, 30, 45, 60)min, 2 hours, 3hours, 4 hours and 5 hours.

Melting point determination

One of the physical tests that are required for characterization of cilostazol precipitate is the melting point.The melting point was between 158-160˚C which is the same as for that for pure one[18].

Differential scanning calorimetry (DSC)

The DSC thermogram of the pure and precipitated cilostazol showed a sharp peak at 163.88˚C and 164.14˚C respectively (figure 6) that is the same as that for pure one [19], so no change in the drug state and no interference from the added excipient.



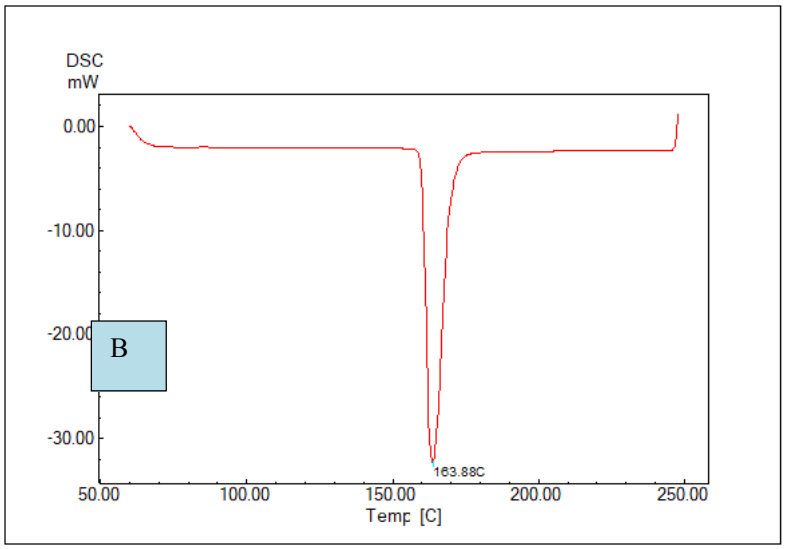


Fig.6: DSC thermogram of [A] pure cilostazol, [B] precipitant.

FTIR spectroscopy

The FT-IR spectrum of pure cilostazol powder and cilostazol precipitatewere identical, as shown in Figure (7).

Cilostazol shows its characteristic peaks at 2936.52cm^{-1} and 2872.01 cm^{-1} assigned to stretching vibration(-CH_2-)group, 2668.43 cm^{-1} assigned to (C=O) stretching vibration, 1504.48 cm^{-1} assigned to aromatic double bond stretching vibration, 1242.16 cm^{-1} assigned to asymmetric stretching vibration of aromatic ether and 1037.7 cm^{-1}assigned to symmetric stretching vibration of aromatic ether[20].

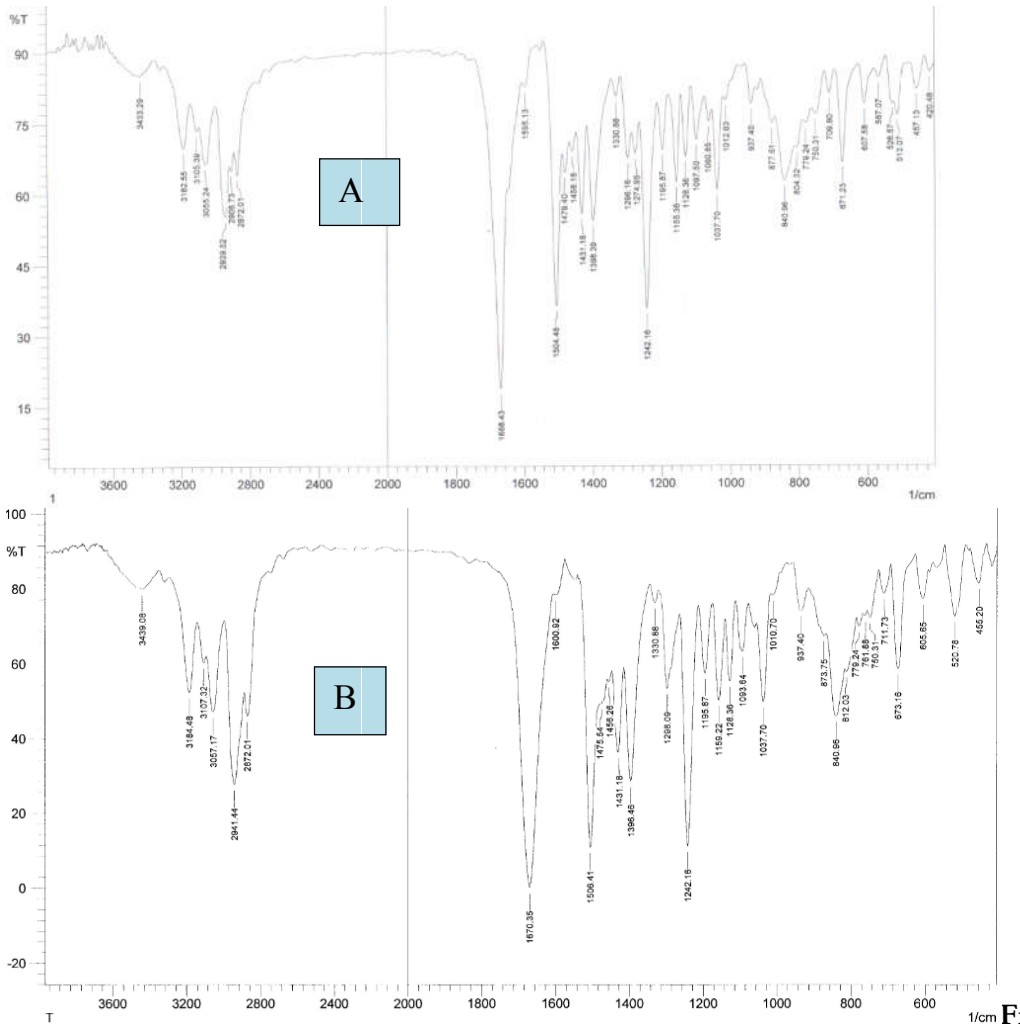


Fig.7: FT-IR spectrum of cilostazol. [A] pure powder [B] precipitate

CONCLUSION:

This study succeeded to prepare cilostazol liquid oral dosage form using supersaturated self-emulsification technology utilizing soluplus with minimum vehicle ingredients in comparison to liquid SEDD that improve drug solubility, absorption and reducing bioavailability variation with no vehicle-related side effects that will lead to improving patient compliance

ACKNOWLEDGEMENT:

The authours would like to thank department of pharmaceutics in the college of pharmacy,

Mustansiriyah university for this work.

CONFLECT OF INTEREST:

The authors declare no confect of interest

REFERENCES

1. H. CWaK. Clinical Pharmacy and Therapeutics, 6th Edition2015.
2. Porter CJ, Pouton CW, Cuine JF, Charman WN. Enhancing intestinal drug solubilisation using lipid-based delivery systems. Adv Drug Deliv Rev. 2008;60(6):673-91.
3. Wang L, Dong J, Chen J, Eastoe J, Li X. Design and optimization of a new self-nanoemulsifying drug delivery system. J Colloid Interface Sci. 2009;330(2):443-8.
4. Anand U. Kyatanwar KRJ, Vilasrao J. Kadam. Self micro-emulsifying drug delivery system (SMEDDS) : Review. Journal of Pharmacy Research. 2010;3(1):75-83.
5. Dae R.l. MJH, Hyuck J.J., Ha R.C., Jun S.P., et al. Enhanced dissolution and oral absorption of tacrolimus by supersaturable self-emulsifying drug delivery system. International Journal of Nanomedicine. 2016;11:1109–17.
6. Ali N. Wannas NKM. preparation and in-vitro evaluation of cilostazol self-emulsifying drug delivery system. Al-mustansiriyah J of pharm Sci (AJPS) 2019.
7. Quan G, Niu B, Singh V, Zhou Y, Wu CY, Pan X, et al. Supersaturable solid self-microemulsifying drug delivery system: precipitation inhibition and bioavailability enhancement. Int J Nanomedicine. 2017;12:8801-11.
8. Zhong Y, Jing G, Tian B, Huang H, Zhang Y, Gou J, et al. Supersaturation induced by Itraconazole/Soluplus® micelles provided high GI absorption in vivo. Asian Journal of Pharmaceutical Sciences. 2016;11(2):255-64.
9. DiNunzio JC, Hughey JR, Brough C, Miller DA, Williams RO, 3rd, McGinity JW. Production of advanced solid dispersions for enhanced bioavailability of itraconazole using KinetiSol Dispersing. Drug Dev Ind Pharm. 2010;36(9):1064-78.
10. Yadav PS, Yadav E, Verma A, Amin S. Development, characterization, and pharmacodynamic evaluation of hydrochlorothiazide loaded self-nanoemulsifying drug delivery systems. ScientificWorldJournal. 2014;2014:274823.
11. The United States Pharmacopoeia (USP) 30. NF28.USA: The United State pharmacopeial convention Inc. ; 2010.
12. Maulik R. Mehta RYM, Chhahan N. Patel Hardik M. Daraji. formulation and evaluation of sublingual tablet of candesartan cilexetil. International Journal of pharmaceutical research and bio-science. 2014;3(2):900-25.
13. Adriano Antunes Souza Araújo MdSB, Sílvia Storpirtis, Jivaldo do Rosário Matos. Determination of the melting temperature, heat of fusion, and purity analysis of different samples of zidovudine (AZT) using DSC. Brazilian Journal of Pharmaceutical Sciences. 2010;46(1):37-43.
14. Patel PV, Patel HK, Panchal SS, Mehta TA. Self micro-emulsifying drug delivery system of tacrolimus: Formulation, in vitro evaluation and stability studies. Int J Pharm Investig. 2013;3(2):95-104.
15. Ha ES, Choo GH, Baek IH, Kim MS. Formulation, characterization, and in vivo evaluation of celecoxib-PVP solid dispersion nanoparticles using supercritical antisolvent process. Molecules. 2014;19(12):20325-39.
16. Song WH, Park JH, Yeom DW, Ahn BK, Lee KM, Lee SG, et al. Enhanced dissolution of celecoxib by supersaturating self-emulsifying drug delivery system (S-SEDDS) formulation. Arch Pharm Res. 2013;36(1):69-78.
17. Yeom DW, Chae BR, Son HY, Kim JH, Chae JS, Song SH, et al. Enhanced oral bioavailability of valsartan using a polymer-based supersaturable self-microemulsifying drug delivery system. Int J Nanomedicine. 2017;12:3533-45.

18. Stowell GW, Behme RJ, Denton SM, Pfeiffer I, Sancilio FD, Whittall LB, et al. Thermally-prepared polymorphic forms of cilostazol. J Pharm Sci. 2002;91(12):2481-8.
19. Hitesh K Patel PVP, Chetan K Misan, Dhaval S Mehta, Mandev B Patel. Development and characterization of liquid and solid self-microemulsifying drug delivery system of Tacrolimus. Asian Journal of Pharmaceutics 2012:204-11.
20. Nidhi H. Upadhyay SKSaDJP. Formulation development and characterization of directly compressible tablets of cilostazol loaded spherical crystal agglomerates. WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES. 2018;7(5):1118-36.