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COMPARATIVE STUDY OF SOLUBILITY AND DISSOLUTION ENHANCEMENT OF LACIDIPINE USING SYNTHETIC AND NATURAL SURFACTANTS

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ABSTRACT

In modern era a major concern associated formulation development by using synthetic new chemical entities is their poor water solubility which poses problems of low oral bioavailability. Lacidipine is an antihypertensive drug, classified as a class II drug is one such example with low solubility and hence low oral bioavailability. In present work successfully attempt has been made to carry out a comparative study of solubility and dissolution enhancements of Lacidipine using SLS as synthetic and saponine extracted from soya bean as natural surfactants. At 1.5% of SLS and saponine solubility enhancement shown by Lacidipine in aqueous medium was 25.95 and 42.64 mg/ml compared to 0.55 mg/ml. Added advantage of saponine is it has lipid lowering capability. So a formulation developed using combination may show better management of hypertension.

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INTRODUCTION

In modern era of synthetic drugs, new synthetic chemical entities are found to be associated with poor water solubility which adversely affects their use via oral route of administration due to decreased bioavailability. Developing a formulation for poorly water-soluble drugs has always been a challenge for formulation development scientists. Previously in initial stages of drug discovery substantial importance was given to Leppink's rule of five, but nowadays it is found that approximately 40% of all drugs currently in market, and 90% of the compounds at the development stage are reported to show poor water solubility. This has led to generation of Biopharmaceutical Classification System (BCS) for drug and new chemical entities.¹⁻³

To overcome the challenge of formulation development for BCS class drugs categorized under class II and class IV, formulation scientists have discovered and are using various techniques like pH adjustment, lyophilization, evaporative precipitation into aqueous solution, use of surfactant, use of co-solvent, hydrotropy method, use of salt forms, solvent deposition, solubilizing agents, modification of the crystal habit, co-crystallisation, complexation, and drug dispersion in carriers and for the enhancement of the solubility of poorly soluble drugs.²⁻⁴ One of the recent discoveries is, microwave assisted bionanocomposites formulation.³⁻⁶

In case of surfactants as solubility enhancers, the structure of surfactants has two distinct regions, one of which is water-loving or hydrophilic and the other is water-hating or hydrophobic. These compounds have ability to lower the surface tension (or interfacial tension) between two liquids or between a liquid and a solid thereby help in increasing the solubility of poorly water soluble drugs.⁴⁻⁷

In present scenario due to hectic life style and increase use of fast food large population suffering from both hypertension and hypercholesterolemia. These are two most important risk factors for cardiovascular diseases. Normally, use of Statins is done as drugs of choice in treatment of plasma lipid abnormalities and has been reported to interact with elevated blood pressure. There is report of reduction in blood pressure in patients with untreated hypertension and in patients treated with antihypertensive drugs, particularly angiotensin-converting enzyme inhibitors and calcium channel blockers. This effect on blood pressure control has also been observed in diabetic patients. The capacity of statins to improve blood pressure control may represent a useful tool for improvement in the prevention of cardiovascular diseases.

Saponins are categorized as diverse group of compounds which are widely distributed in the plant kingdom, characterized by a triterpene or steroid aglycone and one or more sugar chains in their structure. Use of saponin is also lead to variety of application in food, cosmetic and different pharmaceutical sector. Another advantage of saponin is their biological and anti cholesterol activity which result in emergence of commercially available saponin.⁸

Lacidipine belongs to group of dihydropyridine which act as calcium channel blocker. Chemically, it is diethyl (E)-4-{2-[(*tert*-butoxyl carbonyl) vinyl] phenyl}-1, 4-dihydro-2, 6-dimethyl pyridine -3, 5-dicarboxylate. It exerts antihypertensive action through blocking the influx of Ca ions through voltage gated L-type Ca channel to the peripheral vascular smooth muscle cells, coronary smooth muscle cells and to the myocardial cells. Being a BCS class II drug it suffers from drawback of low aqueous solubility. Consequently, if a drug has low solubility in water or insoluble in water it and thus its permeability will be reduced or will be negligible and can't be absorbed through the membranes.⁹⁻¹⁰

As saponin are having similar properties to synthetic statins, the aim and objective of present work was to use of saponin as natural surfactants and carry out a comparative study of solubility enhancement of Lacidipine a BCS class II drug by using SLS as synthetic and saponin as natural surfactant. In present study an attempt has been made to carry out comparative study of improving solubility and dissolution rate of Lacidipine using surfactants of synthetic and natural origin. Sodium lauryl sulphate is used as synthetic surfactant, whereas saponin isolated from soya seeds was used as natural surfactants. These were selected on the basis of their good surfactant and wetting property. The additional advantage of using saponin as natural surfactant is, it shows lipid lowering characteristic.

MATERIAL & METHOD

MATERIAL

Lacidipine was obtained as gift sample from Unichem pharmaceutical laboratories, Goa and all the chemicals were purchased from SD Fine Chem. Ltd., Mumbai, India. Soya seeds were purchased from local market. All the reagents used were of analytical grade.

METHODS

UV and HPLC methods were developed to carry out comparative dissolution and solubility enhancement study. For UV selection and identification of correct wavelength is of prime importance. In present study, the λ_{\max} (wavelength at which maximum absorbance is seen) for solution of Lacidipine exposed to UV range of 200 to 400 for the solubility and dissolution enhancement was found to be 240 nm.

EXTRACTION OF SAPONINE FROM SOYA SEEDS

For extraction of saponin first step were pretreatment steps in the form of drying, particle size reduction, and defatting. Use lipophilic solvent, such as ethyl acetate as well as *n*-hexane was done for defatting.

The pretreated powdered material was extracted with the use of Soxhlet apparatus using methanol as solvent. The process was carried out for 48 hr. It gave sticky product. Process of evaporation was used to further remove solvent and the lyophilization was done to get free flowing powder. The obtained powder of saponin was used as natural surfactant in solubility and dissolution enhancement study.

SOLUBILITY STUDY

Phase Solubility Study is a preliminary requirement for evaluation of affinity between the ligand and drug. Study was carried out using different solvents like water, methanol, isopropyl alcohol, phosphate buffer solution (PBS pH 6.8 and pH 7.4) and 0.1 N HCL as per Method reported by Higuchi and Connors (Higuchi and Connors, 1965).

Solubility study was conducted by adding excess of drug to vehicle and mixture was shaken for 24 hrs in orbital shaker. After achieving equilibrium, about 5ml samples were withdrawn and filtered through filter paper, it was then suitably diluted and absorbance was recorded at 240nm. The absorbance readings were used to carry out calculation of concentration of Lacidipine.

FORMULATION AND EVALUATION OF LACIDIPINE ORAL DISINTEGRATION TABLET

ODTs of LCDP were prepared by direct compression method. Different concentration of synthetic as well as natural surfactant as 0.5%, 1%, 1.5%, 2% were utilized in formulation of tablet dosage form. Sodium lauryl sulphate (SLS) was used as synthetic surfactant while saponine extracted from soya seeds was used as natural surfactant. Other excipients were used as per mentioned in table no.1. The final mixture was compacted using a single punch-tablet machine.

Table1: List of Excipients for Orodispersible Tablet.

Sr. No.	Ingredients	Qty. taken	Activity
1	Lacidipine	4 mg	API
2	Sodium lauryl sulphate	0.5% 1%	Synthetic surfactant
3	saponine	1.5% 2%	Natural surfactant
4	Lactose monohydrate	75 mg	Diluents
5	Magnesium stearate	5 mg	lubricant
6	Crosscarmallose sodium	15 mg	superdisintegrants
Total		100 mg	

EVALUATION OF TABLETS

Pre compression studies

Bulk Density

Apparent bulk density (ρ_b) was determined by pouring the powder blend into a graduated cylinder. The bulk volume (V_b) and weight of powder (M) was determined. The bulk density was calculated using the formula.

Bulk density = Mass of powder / Bulk volume

$$D_b = M / V_o$$

Tapped Density

It is the ratio of total mass of powder to the tapped volume of the powder.

Tapped Density = Mass of powder / Tapped volume

$$D_t = M / T_v$$

Angle of Repose

The flow ability of powdered blend of all the batches was assessed by the angle of repose. The angle of repose was determined by using fixed funnel free-standing cone method. Angle of repose was determined in triplicate for all the batches by using the formula,

$$\begin{aligned} \tan \theta &= H/R \\ \theta &= \tan^{-1}(H/R) \end{aligned}$$

Where, ' θ ' is angle of repose; 'H' is height between lower tip of the funnel and the base of heap of powder; and 'R' is radius of the base of heap formed (Jadhav et al; 2010).

Carr's compressibility index

Powdered Blend of all the batches were evaluated for Carr's compressibility index (CCI) and Hausner's ratio (HR). Bulk density apparatus was used for tapping (Lab Hosp, Mumbai, and Maharashtra, India). Where, TD and BD are tapped density and bulk density respectively.

Post- compression evaluation of tablets

Hardness and thickness

After preparation of tablets of all the batches were evaluated for various evaluation parameters like tablet thickness, hardness, weight variation and friability. The thickness was measured by using Vernier caliper while hardness was determined by using Monsanto hardness tester.

Tablet hardness is defined as the force required for breaking a tablet in a diametric compression force. It is also known as tablet crushing strength. The hardness tester used for the study was Monsanto Hardness Tester. It applies the force to the tablet diametrically with the help of a spring. The tester was initially adjusted to zero. Triplicate determinations were done. Thickness was determined with the help of Vernier caliper.

Weight variation

20 tablets were selected at random and average weight was determined. Then the individual tablet was weighed and its weight was compared with average weight. The individual weight of two tablets weight should not be more than percentage given in the following table.

Friability

Friability test was performed to assess the effect of friction and shock which may often causes chipping, capping, or breaking of tablets. The phenomenon in which surface of tablet is damaged or breakage can occur when subjected to mechanical shock. Compressed tablets should not lose more than 1% w/w of their weight (Indian Pharmacopoeia, 1996). This test was carried out to determine loss of weight by using Roche Friabilator. The friability is expressed in percentage (%).

$$F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} * 100$$

% Friability of tablets less than 1% is considered acceptable.

Wetting time

Take 1 filter paper, folded twice according to Petri plate, add 10 ml buffer solution of pH 6.8. Tablet was placed on filter paper and time was recorded for complete wetting was noted.

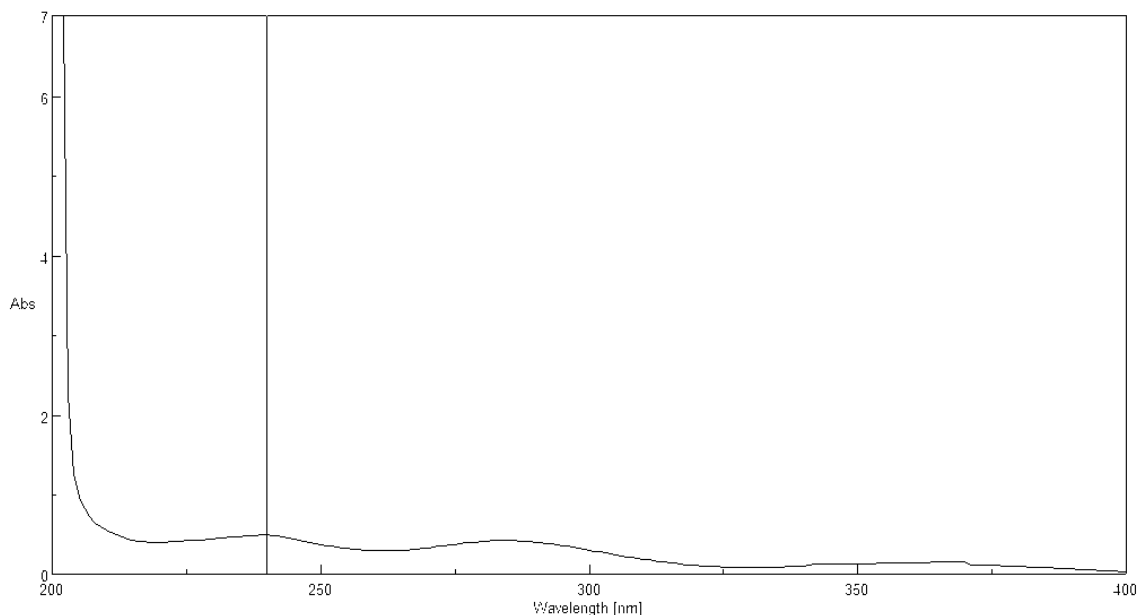
IN-VITRO DISSOLUTION STUDY

The dissolution study was carried out for tablet containing pure LCDP and as well as experimental formulations containing synthetic and natural surfactant for comparison. 900 ml of freshly prepared phosphate buffer of pH 6.8 was placed in each dissolution vessel of dissolution test apparatus (USP, II paddle method). The temperature of the dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$ and the paddles were rotated at 50 rpm. At the specific time intervals of 0, 15, 30, 45, 60 min, 5 ml of sample was withdrawn and the same volume was replaced by fresh media. The withdrawn samples were filtered, diluted and estimated by UV spectroscopy at 240 nm, thereby the cumulative percent drug release at each interval was calculated.

RESULT & DISCUSSION

DETECTION OF WAVELENGTH (λ_{max})

The spectrum was recorded in the UV range of 200 to 400 nm by preparing solution in methanol. The spectrum recorded is shown in Graph 1 and the result is mentioned in Table no.2



Graph 1. UV spectra of Lacidipine.

Absorbance was found to be 0.632

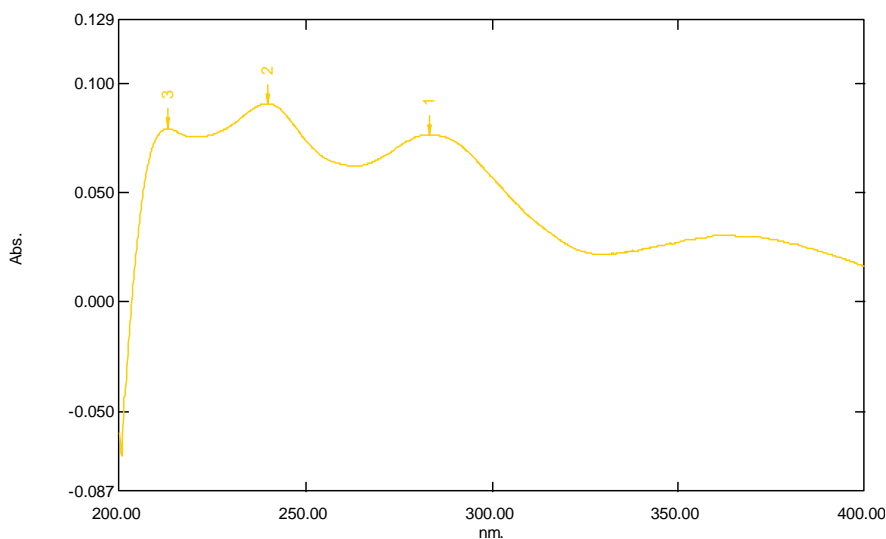
Table2: Absorbance of Lacidipine.

Drug	λ_{\max} (nm)	Absorbance
Lacidipine	240	0.632

SOLUBILITY STUDY

Solubility study by UV method

The solubility of the Lacidipine in different solvents was recorded and phase solubility diagram was drawn, to study relation between the solubility of Lacidipine in presence of different concentrations of synthetic and natural surfactants. Solubility of Lacidipine in water is shown in table 3 while solubility of same in presence of different concentrations of SLS and saponine is shown in detailed in table 4.



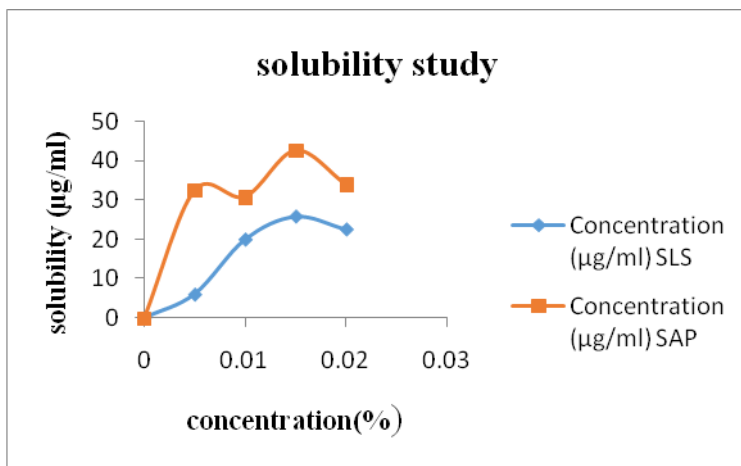
Graph 2: Solubility of Lacidipine in water.

Table 3: LCD aqueous solubility.

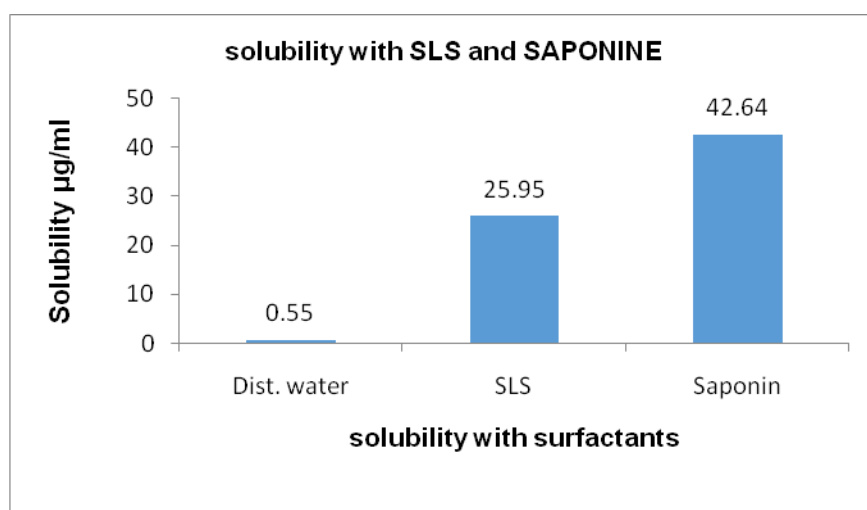
Solvent	Solubility (mg/ml)
Distilled Water	0.55

Table 4: Solubility with surfactants.

Sr. No.	Conc. (%)	Surfactants solubility (mg/ml)	
		Sodium lauryl sulphate	Saponine
1)	0.5 %	6.10	32.51
2)	1%	20.10	30.85
3)	1.5 %	25.95	42.64
4)	2 %	22.67	34.00



Graph 3. Comparative solubility study of LCD with SLS and Saponine.

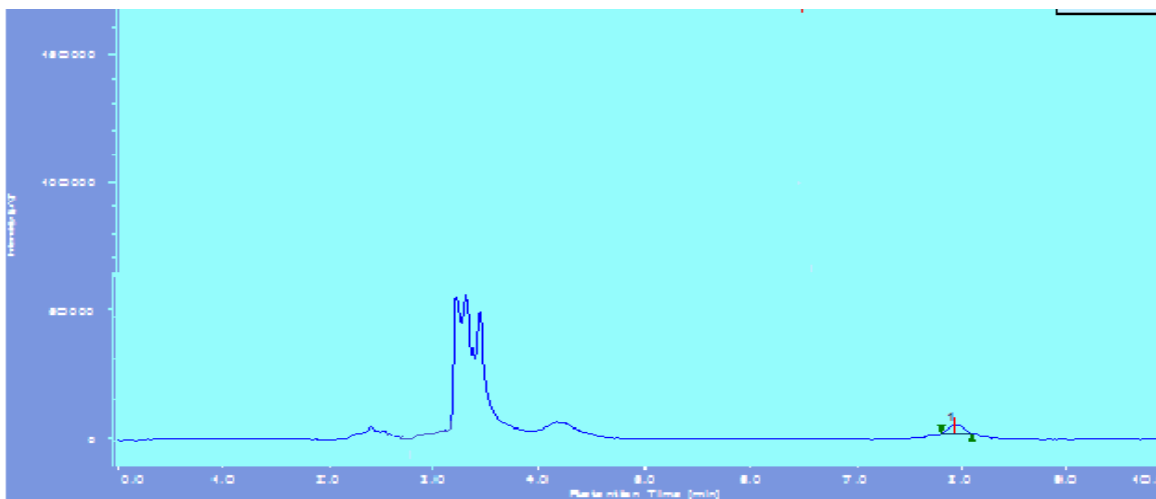


Graph 4. Graphical representation of comparative solubility study of LCDP in SLS and saponine.

From the above results, it can be confirmed that solubility of Lacidipine in water is improved by use of both synthetic and natural surfactant. For both surfactants at concentration of 1.5% w/v highest solubility is observed. It is also observed that use of saponine has shown greater solubility enhancement of Lacidipine in water compared to SLS.

SOLUBILITY STUDY OF LCD BY HPLC METHOD:

Phase solubility study of LCD was carried out according to Higuchi and Connors method, 1965. Based on solubility and surfactants selection of UV data, saponine and sodium laurel sulphate are selected as a surfactants for the enhancement of solubility and dissolution. Different concentration of both synthetic as well as natural surfactants leads to enhancement of solubility as compared to aqueous solubility. Graph 5 shows the chromatogram of LCD in water.



Graph 5. Chromatogram of LCD in water.

The solubility of LCD in water was found to be $0.45\mu\text{g/ml}$ from calibration data which is given in table 5. Addition of surfactant in concentration like 0.5%, 1%, 1.5% and 2% leads to improvement in solubility.

Table 5: Solubility of LCD in water.

Solvent	Solubility($\mu\text{g/ml}$)
water	0.45

At concentration 1.5% of both the surfactants, highest solubility is observed as compared to aqueous solubility. Figure 6 and 7 shows chromatogram of LCD with saponine and SLS at 1.5%.

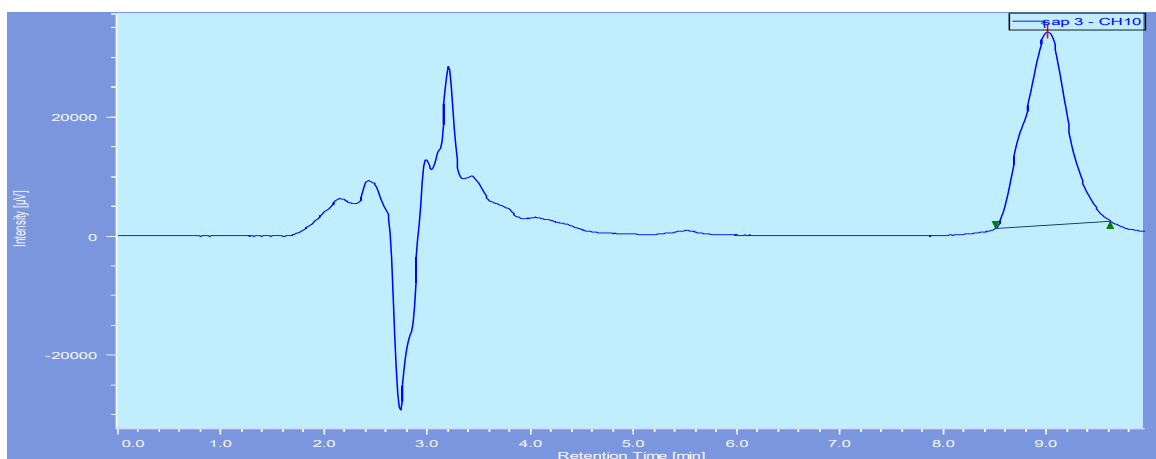


Figure 6. chromatogram of LCD with saponine (1.5%).

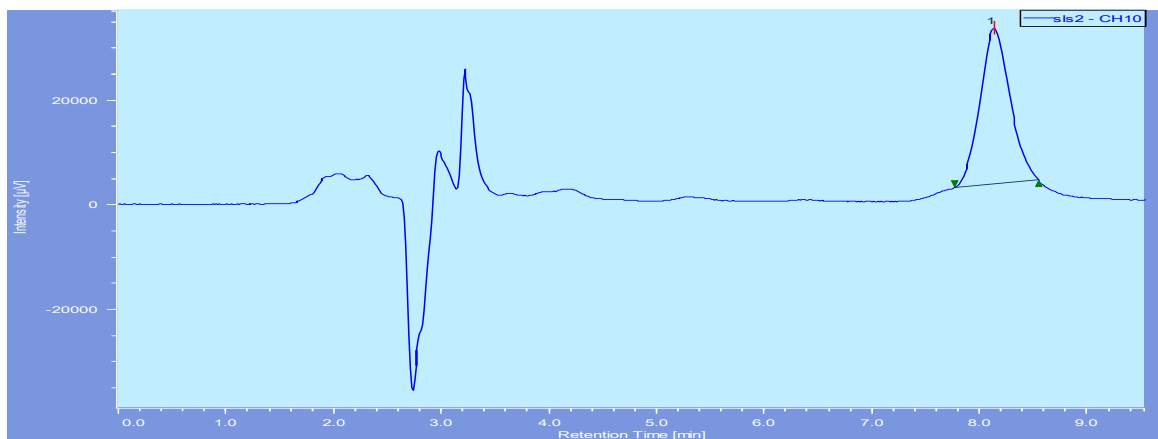


Figure 7. Chromatogram of LCD with SLS (1.5%).

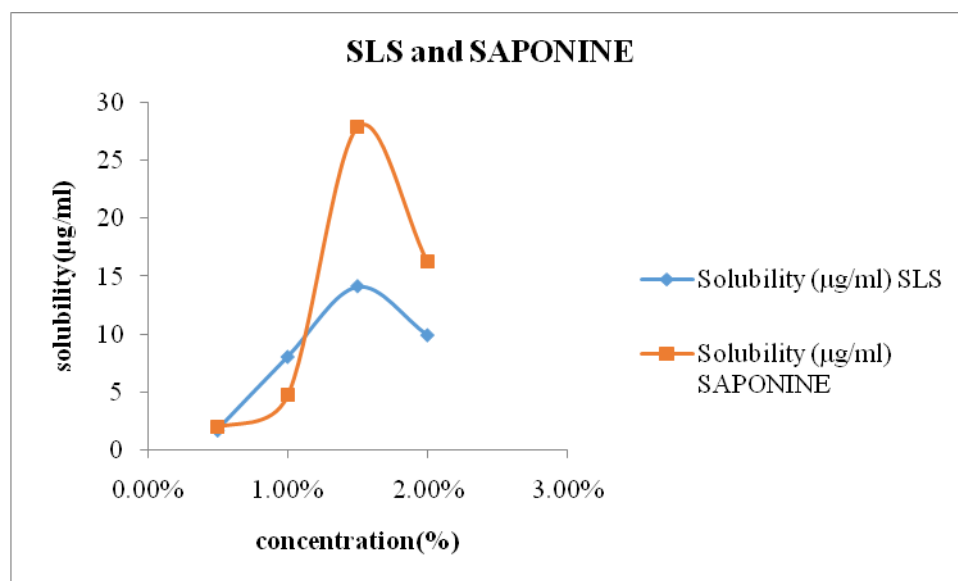


Figure 8 . Comparative solubility study of SLS and SAPONINE.

From the above graph, it can be concluded that solubility of LCD was improved with the help of synthetic and natural surfactant SLS and SAPONINE respectively. At concentration 1.5% both the surfactants showed highest solubility as compared to 2% conc. of SLS and SAONINE. Table5 shows solubility of LCD with saponine and SLS and graphically, it is represented in figure 8.

Table 6: Solubility of LCD at different concentration.

Conc.(µg/ml)	Solubility (µg/ml)	
	SLS	SAPONINE
0.5%	1.75	1.99
1%	8.06	4.72
1.5%	14.12	27.85
2%	9.92	16.22

FORMULATION AND EVALUATION OF LACIDIPINE ORAL DISINTEGRATION TABLETS

ODTs of LCDP were prepared by direct compression method. Different concentration of synthetic surfactant and natural surfactant (0.5%, 1%, 1.5%, 2%) was added to prepare a tablets. It is decided from the data obtained from solubility study. SLS is used as synthetic surfactant and saponine from soya seeds is used as natural surfactant.. Lactose monohydrate is used as diluent. The mixture was mixed gently for 2-3 min. Finally, a 6 % w/w of croscarmellose as a superdisintegrant was added and mixed for 10 min then 1 % w/w of magnesium stearate as a lubricant was added into the mixture and mixed for 2 min. The final mixture was compacted using a single punch-tablet machine.

EVALUATION OF LCD TABLETS

Pre-compression evaluation parameters

Table 7: Pre-compression evaluation of LCD tablets.

Formulation code	Bulk density g/cc	Tapped density g/cc	Angle of Repose Θ	Carr's compressibility index	Flow characteristics
F1	0.51±0.07	0.65±0.01	27.36±0.20	20.5	Good
F2	0.52±0.06	0.63±0.01	30.46±2.08	17.46	Good
F3	0.75±0.08	0.85±0.01	32.08±0.96	11.7	Passable
F4	0.54±0.07	0.64±0.02	30.46±2.08	11.7	Good
F5	0.50±0.07	0.67±0.01	28.42±1.48	17.91	Good
F6	0.54±0.07	0.66±0.02	29.5±0.97	18.18	Good
F7	0.77±0.08	0.88±0.02	31.20±0.88	12.5	Passable
F8	0.49±0.06	0.61±0.01	28.04±1.34	19.67	Good
F9	0.52±0.08	0.63±0.01	27.94±0.52	17.4	Good

Post-compression evaluation parameters

Table 8: Pre-compression evaluation of LCD tablets.

Formulation Code	Hardness (Kg/cm ²)	Friability (%)	Thickness (mm)	Weight variation (Mg)	In-vitro Disintegration time (Sec)	Wetting time (Sec)	Drug content (%) by UV method.
F1	4.4±0.59	0.68±0.52	2.4±0.48	92±0.32	62±0.57	63±0.64	37.90
F2	4.0±0.02	0.67±0.38	2.4±0.59	93±0.31	65±0.26	62±0.37	48.73
F3	4.2±0.64	0.72±0.63	2.5±0.81	96±0.17	73±0.64	48±0.53	62.02
F4	4.8±0.55	0.69±0.61	2.3±0.65	94±0.46	67±0.91	59±0.54	87.38
F5	4.0±0.02	0.71±0.41	2.5±0.87	94±0.68	65±0.58	63±0.59	36.73
F6	4.5±0.75	0.65±0.53	2.4±0.72	95±0.89	69±0.91	61±0.68	48.30
F7	4.3±0.02	0.73±0.41	2.6±0.57	96±0.56	75±0.47	45±0.65	60.79
F8	4.0±0.01	0.70±0.44	2.4±0.61	102±0.53	68±0.96	62±0.55	73.39
F9	4.5±0.02	0.70±0.43	2.7±0.07	98±0.82	72±0.53	63±0.64	48.18

Table 7 and 8 represents results of pre and post evaluation parameters like bulk density, tapped density, untapped density and angle of repose, hardness, thickness, friability test, wt. variation, disintegration time etc. carried out on LCD oral disintegrating tablets. It was observed that all the parameters are passed by LCD tablets.

IN-VITRO DISSOLUTION STUDY

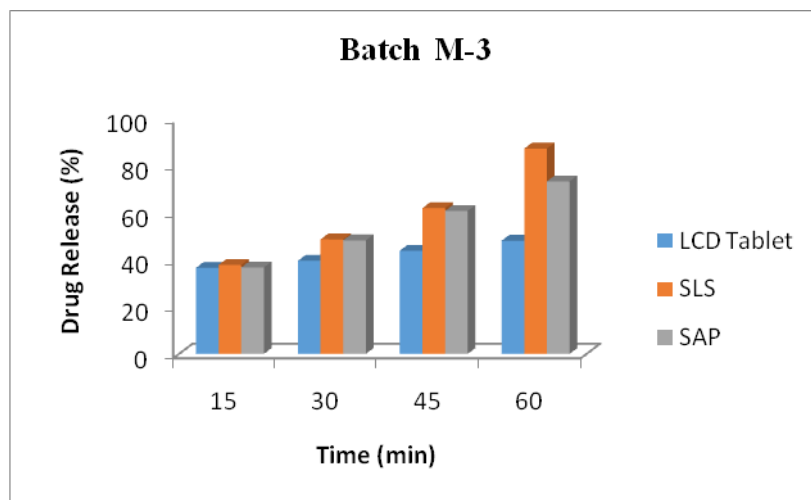
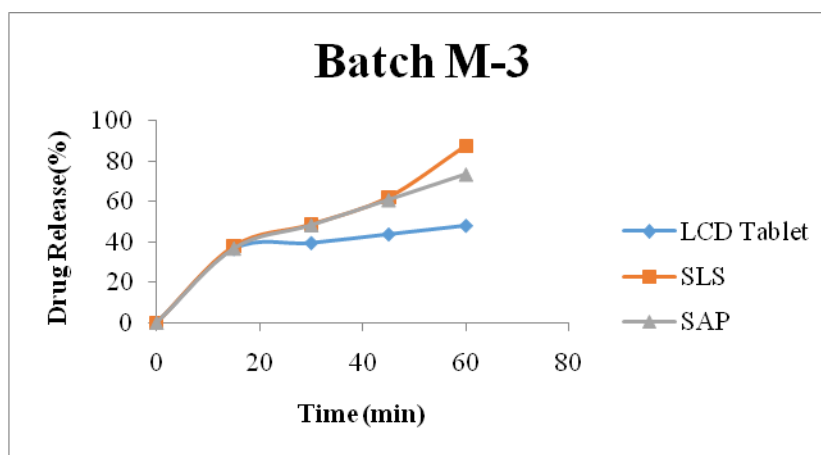
The amount of *in vitro* drug released at different time intervals are plotted against time to obtain the dissolution profiles. Comparative results of formulation with plane Lacidipine and Lacidipine with SLS and saponine are mentioned in Table no. 9. Samples were withdrawn at 15, 30, 45 and 60 min time interval. At the end of 60 min time interval, pure drug show maximum drug release of 48.18 % whereas, formulation of optimized batch with SLS 1.5% show drug release of 87.38% while for batch with 1.5% saponine it was 73.39%. From the results of % drug release and comparative study though it is observed that, batch 1.5% SLS show highest drug release, a very comparable % drug release has been observed for a batch with 1.5% saponine. In comparative study it can be seen that there is a substantial increase in % drug release in batch where use of saponine. The results are mentioned in Table no. 10

Table 9: Results of comparative % drug release study after 60 min.

Batches	LCD	SLS	SAP
M-1 (0.5%)	48.60 %	85.18%	71.08%
M-2 (1%)	48.60%	85.83%	72.12%
M-3 (1.5%)	48.60%	87.38%	73.39%
M-4 (2%)	48.0%	86.85%	72.79%

Table 10. *In-vitro* drug release (%) of batch M-1, M-2, M-3 and M-4.

Batches	LCD Tablet	SLS	SAP
M-1	36.64	37.90	36.78
M-2	39.61	48.73	48.30
M-3	43.91	62.02	60.79
M-4	48.18	87.38	73.39

Figure 9. *In-vitro* (%) drug release of batch M-3.Figure 10. *In-vitro* (%) drug release of batch M-3.**In-vitro drug release study using HPLC method:**

In-vitro dissolution kinetics of Lacidipine was carried out by using United States Pharmacopeia (USP) Type-II dissolution test apparatus. The dissolution medium used was 900 ml of distilled water and phosphate buffer (pH6.8) maintained at $37.5 \pm 0.5^\circ\text{C}$. The paddle speed was kept constant at 75 rpm. Samples of 5 ml were withdrawn at specific time interval. The withdrawn samples were diluted and analyzed by HPLC (Jasco MD-2010) in phosphate buffer (pH6.8). The chromatographic mode and conditions are listed in table 11

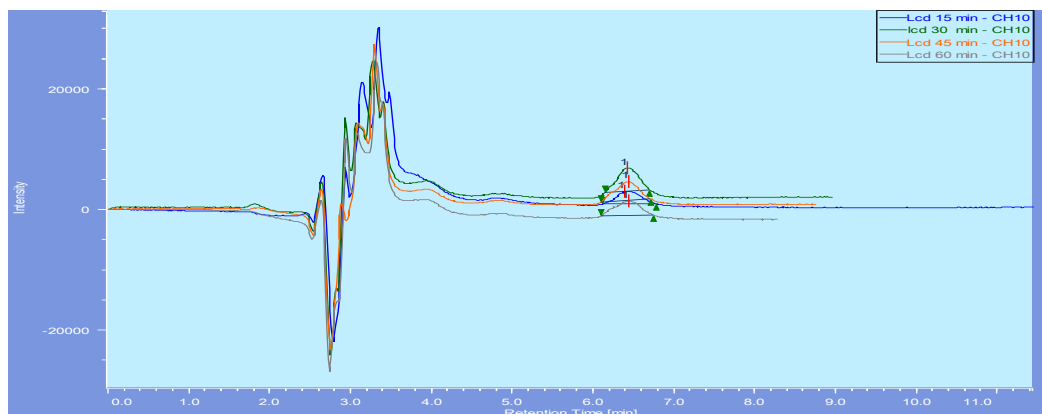
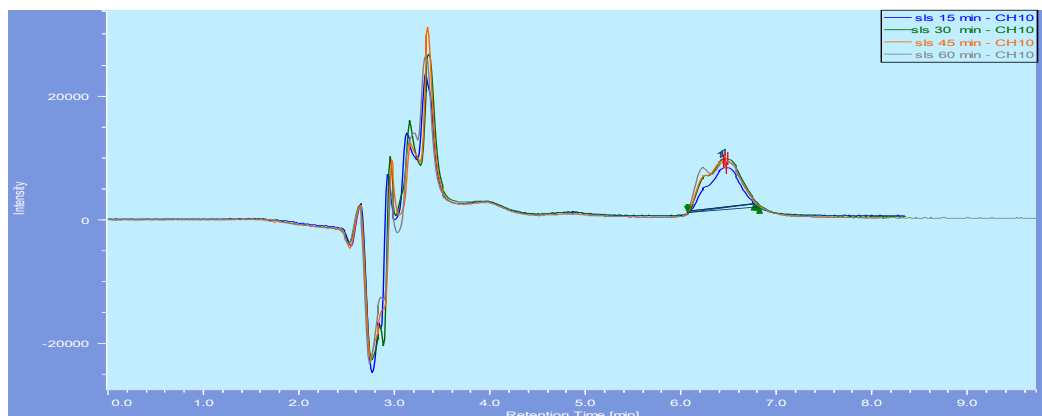
Table11: Mode and conditions for HPLC analysis.

Chromatographic mode	Chromatographic condition
Instrument used	Jasco-HPLC with Pump 2080 Plus, Detector MD 2010
Stationary phase	KYA TECH HIQ Sil C18 (4.6 mm × 250 mm) 5 μm
Mobile phase	Methanol : Water (90:10)
Standard solution	50μg/ml of Lacidipine
Detection wavelength	240 nm
Flow rate	1 ml/min
Sample size	20 μL
Run time	10 min

For HPLC, optimized batch (Batch M-3) is selected from the solubility and dissolution data of LCD by UV method. Samples were withdrawn at regular interval 15, 30, 45 and 60 min respectively, suitably diluted and injected in injector of HPLC-DAD. Runtime given for samples is 10 min and retention time of LCD was found to be 6.4 with 1ml/min flow rate. Table No. 12 showed the % drug release of LCD with SLS and saponine.

Table 12: % drug release of LCD with SLS and saponine.

Time (min)	Drug Release (%)		
	LCD	SLS	SAP
15	33.58	34.60	36.06
30	39.76	41.04	39.50
45	49.01	55.30	53.79
60	52.57	71.25	66.90

**Figure 11: chromatogram of LCD tablet peak overlay.****Figure 12. Chromatogram of LCD with SLS tablet peak overlay.**

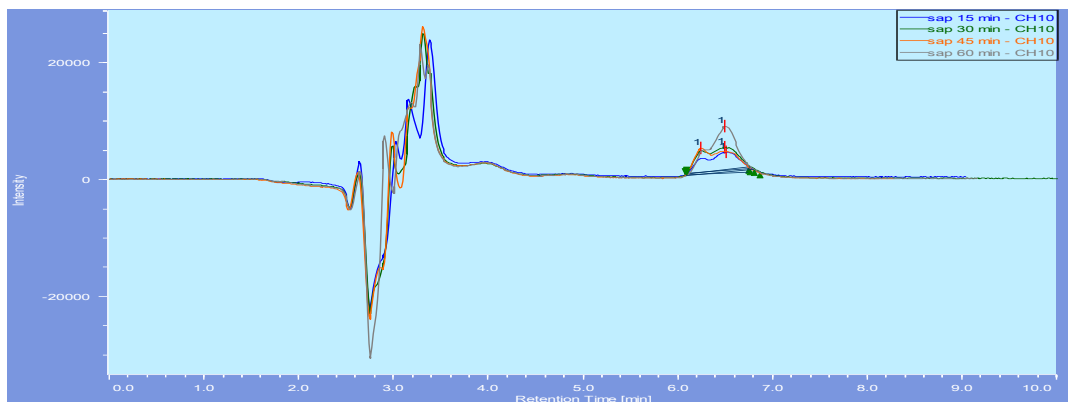


Figure 13. Chromatogram of LCD with SAP peak overlay.

Figure 11 showed chromatogram of Plain LCD tablet, figure 12 showed chromatogram of LCD with SLS and figure 13 showed the chromatogram of LCD with saponine.

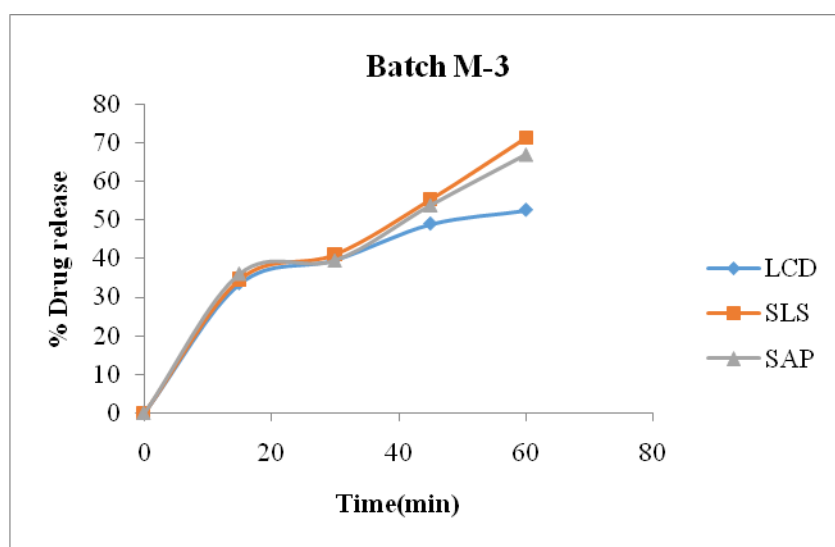


Figure 14. In-vitro comparative study of LCD, SLS and SAPONINE.

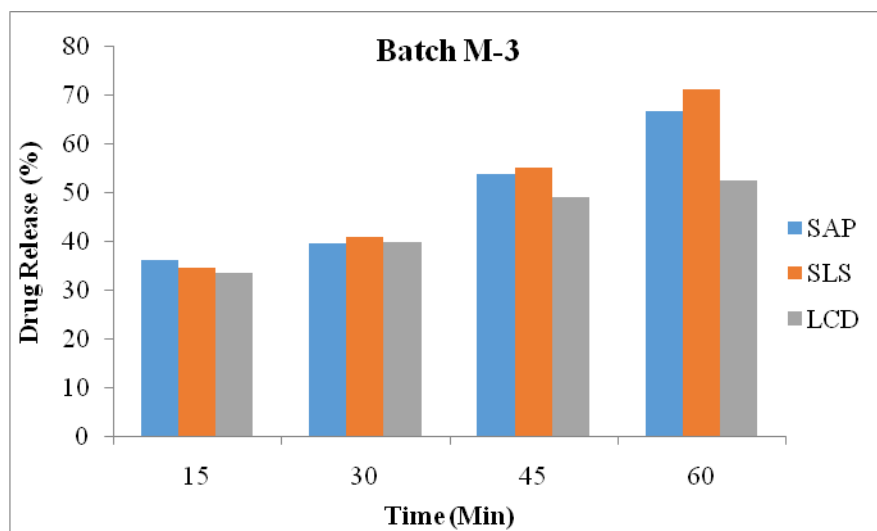


Figure 15 . In-vitro comparative study of LCD, SLS and SAPONINE.

In above figures, graphical representation of dissolution studies of plain LCD, LCD with SLS and LCD with Saponine.

SUMMARY

Dissolution and solubility of drug are rate determining step for oral absorption of drug leading to better bioavailability. In case of poorly water soluble drugs, solubility and dissolution are adversely affected; leading to poor the in-vivo bioavailability of drug. Lacidipine a BCS class II drug has low water solubility and hence poor bioavailability. The aim of the present work was to increase the solubility of Lacidipine using synthetic and natural surfactant. SLS was used as synthetic and saponine as natural surfactant. The results of dissolution and solubility enhancement are very encouraging and are as per the design of protocol of the project. In addition saponin shows similar properties to synthetic surfactants, which have lot of side effects. Hence on the basis of results, in future an attempt can be made of developing formulations of BCS class II antihypertensive drugs having synergistic effect with lesser side effects in better control and maintenance of hypertension.

CONCLUSION

The objectives of present work was to enhance the solubility and dissolution of Lacidipine a BCS class II drug using synthetic and natural surfactants. The results show that the attempt is successful. In addition choice of saponine as surfactant was done as they show natural lipid lowering characteristic. From outcome of positive results it can be concluded that in future an attempt can be made to develop formulations of BCS class II antihypertensive drugs having synergistic effect and lesser side effects in better control and management of hypertension.

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