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Preformulation Studies for Diltiazem in Self Emulsifying Drug Delivery

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ABSTRACT

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Preformulation studies strengthen the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation method, improve public safety standards, enhance product quality, facilitate the implementation of new technologies, facilitate policy development and restrictive higher cognitive process. Preformulation studies offer directions for development of alternative of drug form, excipients, composition, organic structure, helps in adjustment of pharmacokinetic and biopharmaceutical properties. the aim of the current study was to consistently investigate a number of the necessary chemical science properties of calcium blocker loaded small particles. before the event of those major dose forms, it's essential that pertain elementary physical and chemical properties of the diltiazem molecule and different divided properties of the drug powder are determined. This data decides several of the next events and approaches in formation development. A per oral extended unharness small particles of calcium blocker was ready . thus before choice of excipients, the preformulation study of drug is completed for self-made formulation of per oral extended unharness small particles. Preformulation studies enclosed solubility, pKa, dissolution, freezing point, assay development,, stability in solid state; bulk density, flow properties, excipient compatibility, entrapment potency, release profile of small particles and Marketed brands of modified release product were investigated.

Keywords: Entrapment, Absorbance, Solubility

Introduction

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system. The wide range of measurements possible provide fundamental information on the material properties of the system under test, so thermal analysis has found increasing use both in basic characterization of materials and in a wide range of applications in research, development and quality control in industry and academia.

Before beginning the formal preformulation programs the preformulation scientist must consider the following factors:-

- The amount of drug available.
- The physicochemical properties of the drug already known.
- Therapeutic category and anticipated dose of compound.
- The nature of information, a formulation should have or would like to have.

Diltiazem is a nondihydropyridine (non-DHP) calcium channel blocker used in the treatment of hypertension, angina pectoris, and some types of arrhythmia. It relaxes the smooth muscles in the walls of arteries, which opens (dilates) the arteries, allows blood to flow more easily, and lowers blood pressure. Additionally, it lowers blood pressure by acting on the heart itself to reduce the rate, strength, and conduction speed of each beat. Diltiazem has negative inotropic, chronotropic, and dromotropic effects. This means diltiazem causes a decrease in heart muscle contractility – how strong the beat is, lowering of heart rate – due to slowing of the sinoatrial node, and a slowing of conduction through the atrioventricular node – increasing the time needed for each beat. Each of these effects results in reduced oxygen consumption by the heart, reducing angina symptoms. These effects also reduce blood pressure by causing less blood to be pumped out.

Preformulation drug characterization in a structured program:-

Test	**Method/ function Characterization**
FUNDAMENTAL	
1) UV spectroscopy	Simple assay
2) Solubility	Phase solubility/ purity
a) Aqueous	Intrinsic & pH effect
b) pKa	solubility control , salt formation
c) Salt	Solubility, hygroscopicity & stability
d)Solvents	Vehicles & Extraction
e) ko/ w	Lipophillicity, structure activity
f) Dissolution	Biopharmacy
3) Melting point	DSC-polymorphism hydrate & solvent
4) Assay development	UV, HPLC, TLC

5) Stability	
In Solution	Thermal, hydrolysis, pH
In solid state	Oxidation, proteolysis metal ion
Derived	
6) Microscopy	Particle size and morphology
7) Bulk density	Tablet and capsule formation
8) Flow properties	Tablet and capsule formation
9) Compression properties	Acid / excipient choice
10) Excipient compatibility	Preliminary screen by DSC, Conformation by TLC

Quantitative estimation of pure Diltiazem by UV spectrometric method

a) Determination of λmax

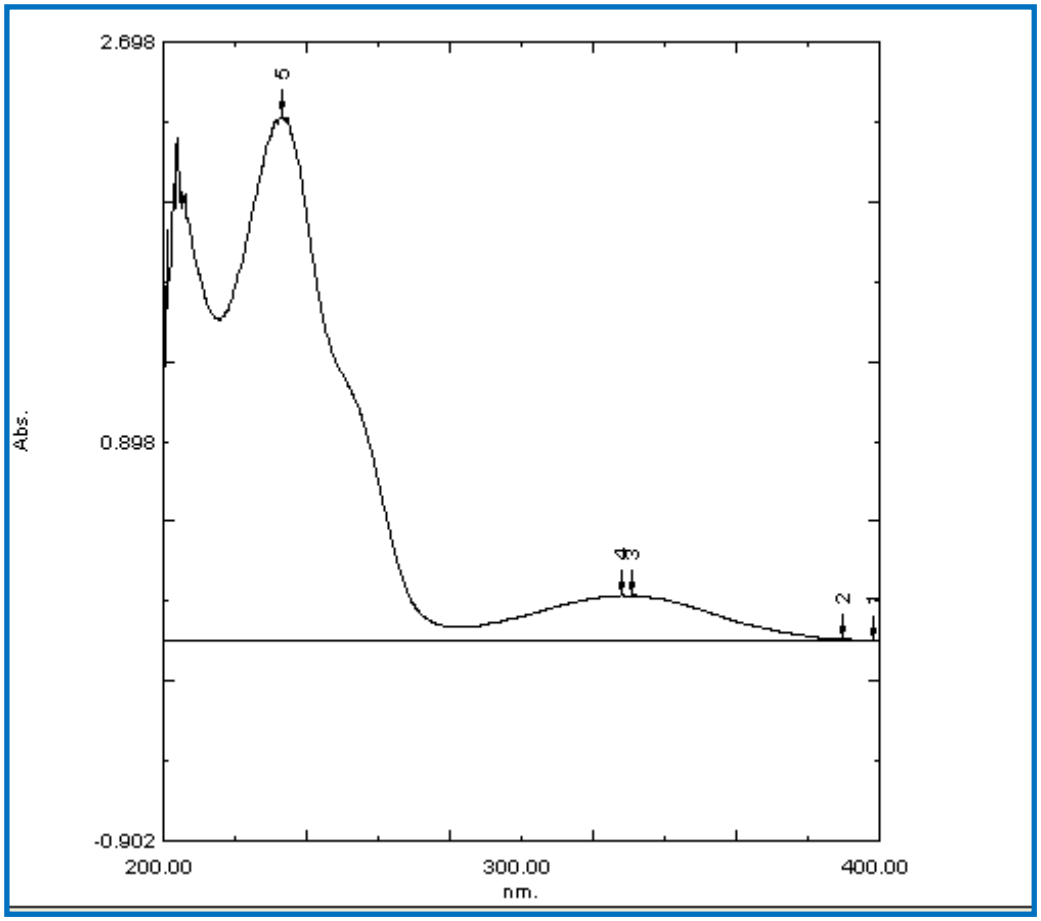


Figure 1: UV SPECTRUM OF DILTIAZEM

Medium **:** 0.01 M methanolic HCl

Standard stock **:** 100 µg/ml

λ_{max} : 237 Diltiazem

Concentration (µg/mL)	Absorbance			Average Absorbance *	S.D (±SD)	Molar Absorptivity (lit/mol.cm)	Sandell's sensitivity (mcg/sq.cm)
	1	2	3				
0	0	0	0	0	0	0	0
5	0.079	0.078	0.076	0.077	0.001528	6499.768	3.60515
10	0.146	0.147	0.150	0.147	0.002082	6178.964	3.792325
15	0.238	0.237	0.241	0.238	0.002082	6657.845	3.2519553
20	0.331	0.332	0.330	0.331	0.001	6925.182	3.383686
25	0.391	0.390	0.396	0.392	0.003215	6566.718	3.568394
30	0.469	0.470	0.468	0.469	0.001	6541.612	3.58209
35	0.554	0.553	0.558	0.555	0.002646	6635.263	3.531532
40	0.641	0.642	0.647	0.643	0.003215	6729.91	3.481865
45	0.723	0.721	0.725	0.723	0.002	6722.936	3.485477

50	0.81 1	0.81 2	0.81 0	0.811	0.001	6787.097	3.452528

b) Standard Calibration Curve of DILTIAZEM by UV-Visible spectrophotometry

The absorbance, standard deviation, molar absorptivity and sandell's sensitivity of DILTIAZEM is as shown in

the table 16.

The Standard calibration curve of DILTIAZEM was obtained in 0.01 M methanolic HCl at 237 Diltiazem, using

TABLE 1: Calibration Curve Data of Diltiazem

*****Average of 3 determinations

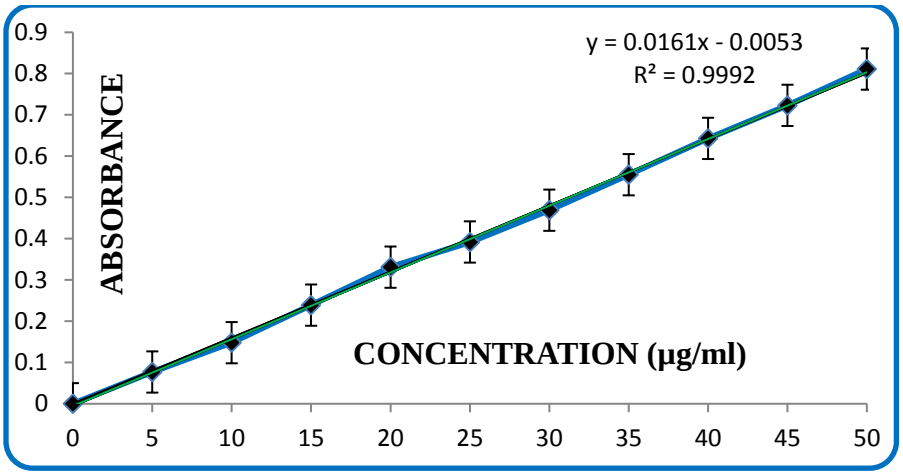


Figure 2: Standard Calibration Curve of DILTIAZEM

Medium : 0.01 M methanolic HCl

Standard stock : 100 µg/ml

λ_{max} : 237 Diltiazem

Beer Lambert's range : 5-50 µg/ml

Regression coefficient : 0.9992

Molar absorptivity : 6534.529 lit $mol^{-1}cm^{-1}$

Sandell's sensitivity : 3.5135 mcg/sq.cm

c) Intra-Day Variability of DILTIAZEM

The R^2 value for intra-day variability of DILTIAZEM is 0.9972.

TABLE 17: Intra-day Variability of DILTIAZEM

Concentration (µg/mL)	Average Absorbance*	± S.D	Molar Absorptivity (lit/mol.cm)	Sandell's sensitivity (mcg/sq.cm)
0	0	0	0	0
5	0.0821	0.001689	6862.416	3.292683
10	0.1492	0.002235	6234.756	3.624161
15	0.2416	0.002215	6722.936	3.360996
20	0.3428	0.003489	7155.324	3.157895
25	0.4027	0.001125	6728.515	3.358209
30	0.4782	0.002452	6667.144	3.389121
35	0.5316	0.003234	6348.333	3.559322
40	0.6471	0.002125	6695.04	3.375
45	0.7213	0.004632	6695.04	3.375
50	0.8073	0.001125	6753.622	3.345725

***Average of 3 determinations

d) Inter-Day Variability of DILTIAZEM

The R^2 value for inter-day variability of DILTIAZEM is 0.9965.

TABLE 2: Inter-day Variability of DILTIAZEM

Concentration (µg/mL)	Average Absorbance*	± S.D	Molar Absorptivity (lit/mol.cm)	Sandell's sensitivity (mcg/sq.cm)
0	0	0	0	0
5	0.0808	0.003256	6761.99	3.341584
10	0.1586	0.001563	6636.458	3.404792
15	0.2442	0.004215	6812.203	3.316953
20	0.3582	0.002354	7494.26	3.015075
25	0.414	0.003125	6929.366	3.26087
30	0.4908	0.005235	6845.678	3.300733
35	0.533	0.004128	6372.243	3.545966
40	0.6454	0.005321	6751.529	3.346762
45	0.735	0.002146	6834.52	3.306122
50	0.8148	0.003165	6818.898	3.313697

*Average of 3 determinations

Standard curve by reverse phase high performance liquid chromatographic (HPLC) method:

Standard curve of DILTIAZEM in Mobile Phase by HPLC

The HPLC conditions for the analytical method developed were as follows:

Instrument: Shimadzu LC-2010 HT, quartenary pumps and UV-Visible SPD M20A detector with auto sampler.

Analytical Column: Phenomenex C-18, (250 mm × 4.6 mm, 5 µ)

Mobile phase: Methanol:Acetonitrile:water (30:40:30% v/ v).

Detection: Wavelength at 276 Diltiazem

Detector: UV-Visible SPD M20A

Flow rate: 1.0 ml/min

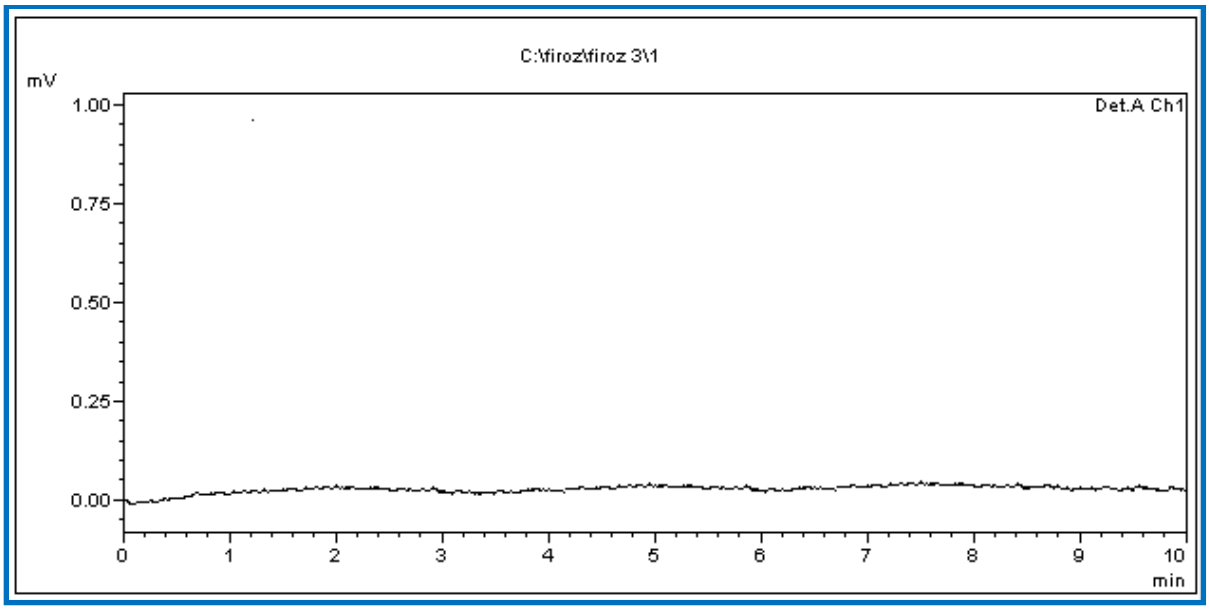


Figure 3: Blank spectra in mobile phase

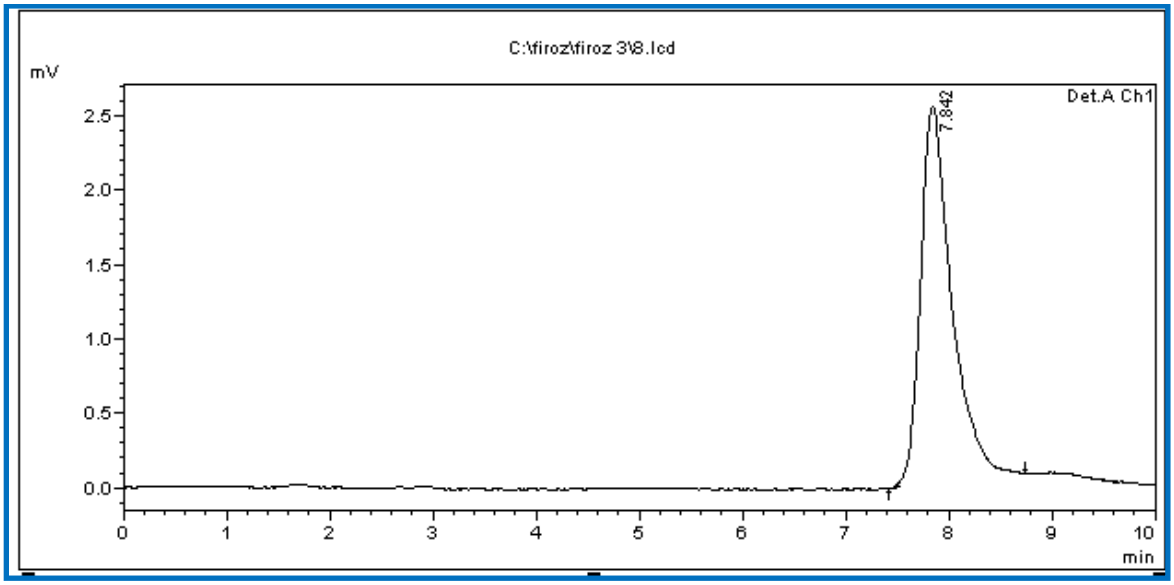


Figure 4: Spectra of DILTIAZEM in mobile phase (1000ng/ml)

Table 3: Calibration curve data of DILTIAZEM in mobile phase:

Concentration (ng/ml)	Area (mV)* ± S.D
0	0
200	2246 ± 0.006
400	5971 ± 0.004
600	8756 ± 0.007
800	11470 ± 0.005
1000	13582 ± 0.003
2000	27982 ± 0.005
3000	40678 ± 0.007
4000	53331 ± 0.008
5000	67396 ± 0.006

* Average of 3 determinations

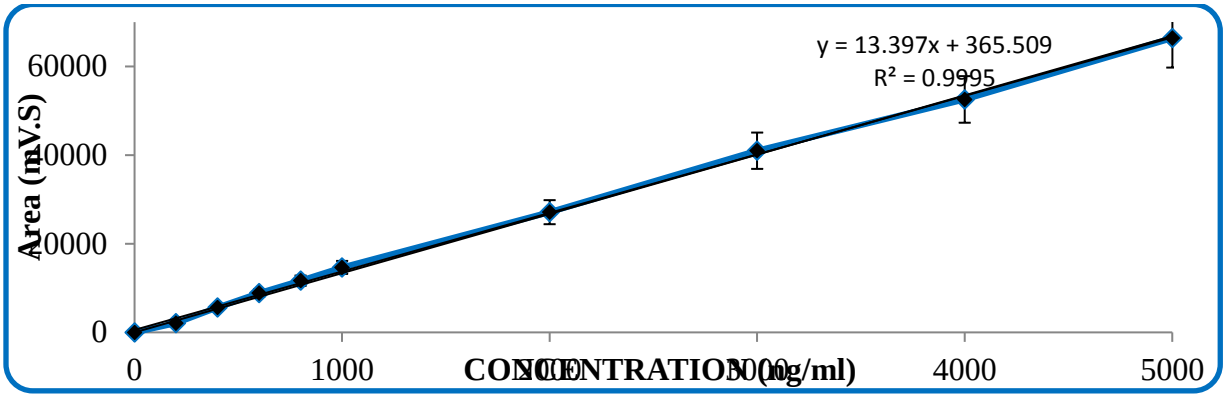


Figure 6: Calibration curve of DILTIAZEM by HPLC method in mobile phase (200-5000ng/ml)

Retention time (R_t) : 7.842 mins

Linearity range : 200ng/ml-5000ng/ml

Regression coefficient : 0.9995

Limit of Detection (LOD) : 180ng/ml

Limit of Quantification (LOQ): 200ng/ml

Table 6: Intraday precision in mobile phase

Concentration (ng/ml)	6th hour	12th hour	18th hour	Deviation	Average	% RSD*
600	9846	9912	10045	101.37	9934.33	0.007
1000	16582	16634	16739	79.98	16651.67	0.003

*Average of 3 determinations

Table 7: Interday precision in mobile phase

Concentration (ng/ml)	Day 1	Day 2	Day 3	Deviation	Average	% RSD*
600	9846	10121	10289	223.64	10085.33	0.008
1000	16582	16746	16912	165.01	16746.67	0.007

*Average of 3 determinations

Table 8: Accuracy of DILTIAZEM by RP-HPLC method

Sl. No.	Level of percentage recovery	Amount of drug present (ng/ml)	Amount of standard drug added (ng/ml)	Amount recovered (ng/ml)	Percentage Recovery	± S.D.*	%R.S.D.	Standard error
1	50	900	450	1330	98.51	0.352	0.3546	0.2034
2	100	900	900	1786	99.22	0.115	0.1150	0.0667

3	150	900	1350	2225	98.88	0.6200	0.6233	0.3580

*Average of 3 determinations

Solubility of DILTIAZEM

Table 9: Solubility of DILTIAZEM in different solvents

Solvents	Solubility(mg/ml)* ±SD
Distilled Water	3.781±0.51
0.01 M methanolic HCl	**6.750±0.45**
pH 1.2 buffer	3.375±0.31
pH 6.8 buffer	3.856±0.39
pH 7.4 buffer	4.312±0.67

*Average of 3 determinations

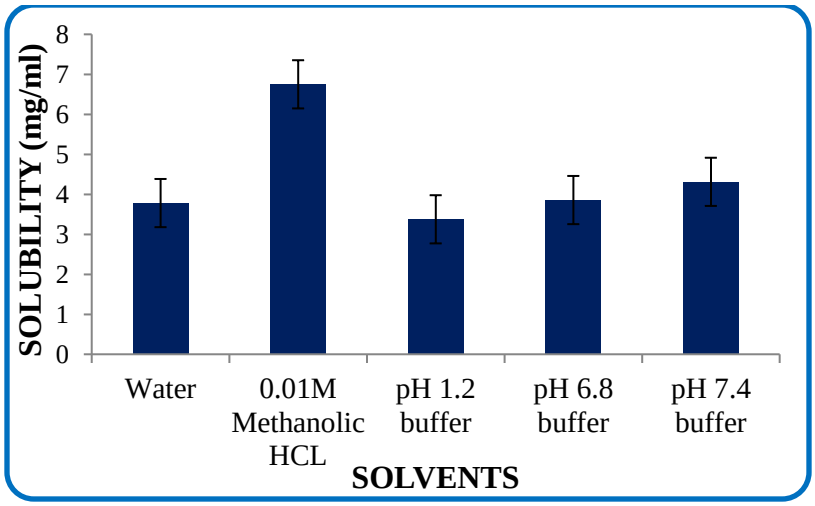


Figure 7: Solubility of DILTIAZEM in different solvents

Partition coefficient of DILTIAZEM

The partition coefficient of DILTIAZEM was found to be 2.14. It is more soluble in organic phase.

. FORMULATION DEVELOPMENT STUDIES

. Selection of SMEDDS Components (Saturation solubility studies)

Table 10: Solubility of DILTIAZEM in few Oils, Surfactants and Co-Surfactants

Vehicle	Function in	Solubility(mg/ml)*

	SMEDDS	±SD
Oleic acid	**Oil**	**23.75±0.25**
Sesame oil	Oil	18.12±0.23
Maisine 35-1	Oil	6.68±0.37
Labrafil M 1944 CS	Oil	10.88±0.32
Cremophor RH 40	**Surfactant**	**22.31±0.26**
Labrasol	Surfactant	13.62±0.29
Tween 80	Surfactant	18.62±0.34
Tween 20	Surfactant	18.12±0.25
PEG 400	**Co-surfactant**	**14.25±0.34**
Span 80	Co-surfactant	8.68±0.25
Lauroglycol 90	Co-surfactant	7.12±0.02
Transcutol P	Co-surfactant	5.93±0.3

*Average of 3determinations

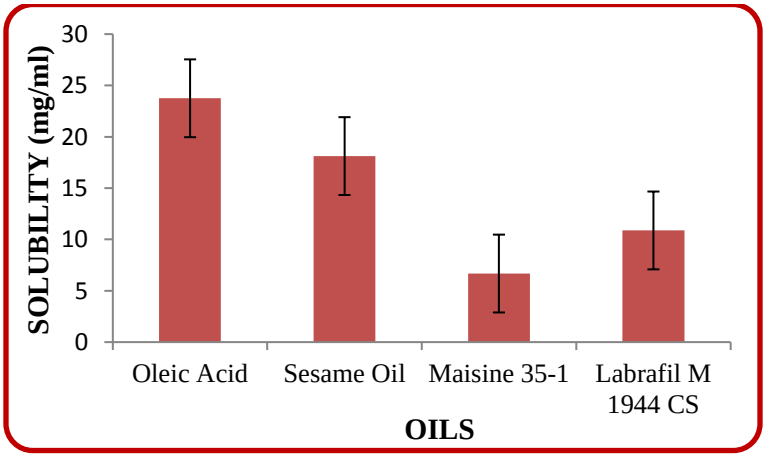
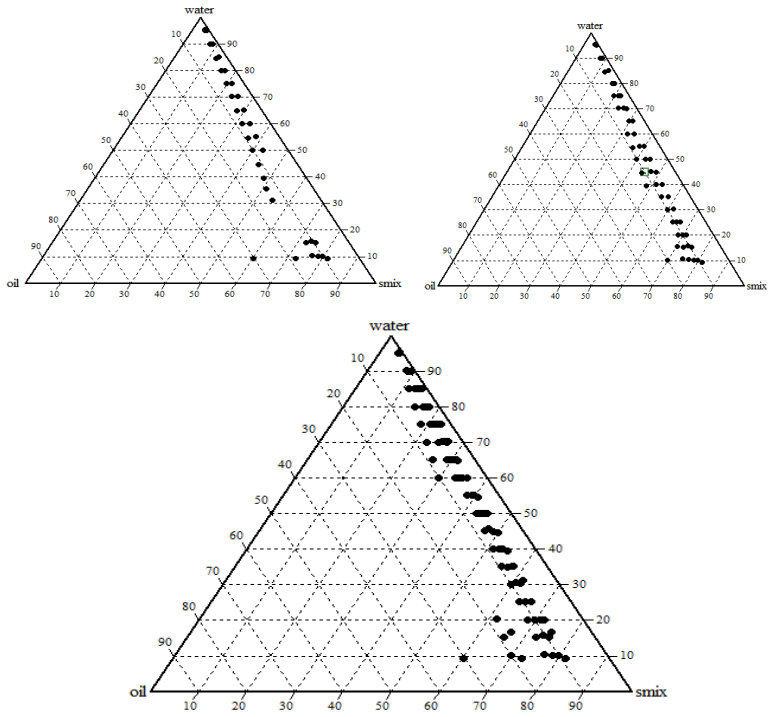


Figure 8: Solubility of DILTIAZEM in different oils

Figure 11: Pseudo ternary phase diagrams in presence of drug with the Smix ratios of 1:1(A), 2:1(B), 3:1(C)

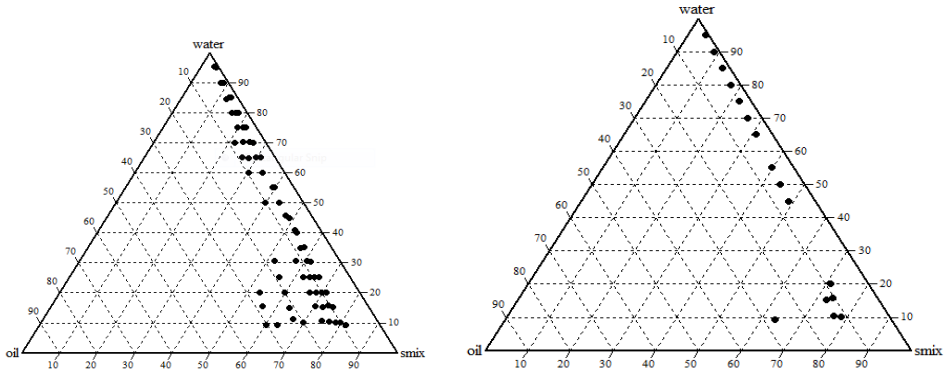


A **B**

C

S_{mix} : 1:1 S_{mix} : 2:1 **S_{mix} : 3:1**

Figure 12: Pseudo ternary phase diagrams in presence of drug with the Smix ratios of 4:1(D) and 1:2 (E)



D **E**

S_{mix} : 4:1 S_{mix} : 1:2

Conclusion

After completion of preformulation evaluation of new drug candidates, it's suggested that a comprehensive report be ready highlight the pharmaceutical issues related to molecules. It helps in developing phase I clinical trial formulations and in preparing regulatory documents and aid in developing subsequent drug candidates. If, drug is found satisfactory sufficient amount is synthesized to perform initial toxicity studies, initial analytical work and initial preformulation.

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