ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
Research Article
www.ijptonline.com

FORMULATION AND EVALUATION OF LIQUISOLID COMPACTS OF FLUNARIZINE HYDROCHLORIDE

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Received on 10-12-2014 *Accepted on 29-12-2014*

Abstract

In recent years with the development of pharmaceutical industry the majority of drug entities synthesized are poorly soluble or water insoluble (class II drugs) due to which the bioavailability of these drugs is very low. Solubility is the major criteria to achieve the desired concentration of the drug in systemic circulation. The aim of present study was to enhance the solubility and bioavailability of flunarizine. Liquisolid technique was chosen to enhance the dissolution properties of Flunarazine.

The Flunarazine liquisolid compacts were prepared by using PEG 400 and Tween 80 as the non volatile liquid vehicles. Avicel PH 102 and Aerosil were used as the carrier and coating material, respectively and 5% sodium starch Glycolate as super disintegrant in each formulation.The final blend was compressed by direct compression method.

The results obtained showed that all the formulations have good flow properties. The FTIR spectra revealed that, there was no interaction between polymer and drug (flunarizine). Post compression parameters such as weight variation, hardness, drug content uniformity, and percentage friability and disintegration time were within the limits of IP standards. The optimized drug (F7) showed hardness 5.3 kg/cm2, friability 0.36%, disintegration time 49 sec and % drug release as 98% in 60 min.. The increase in the dissolution rate was also found to be significant compared to the marketed product. Stability studies showed that there were no significant changes in physical and chemical properties of tablets after 3 months.

Keywords:

Liquisolid compacts, Flunarizine, PEG 400, TWEEN 80, Dissolution rate, Bioavailibility, IP Standards.

1. Introduction

In recent years much attention has been focussed on the problem of drug bioavailability. The solubility of many active pharmaceutical ingredients is one of the technical challenge in formulating a suitable dosage form for efficient drug delivery. Most of the hydrophobic drugs termed as sparingly soluble, slightly soluble and very slightly soluble, undergoes very poor dissolution in the gastro intestinal tract, leading to erratic and incomplete absorption. For these drugs, the dissolution process is the rate-controlling step, which determines the rate and degree of its absorption. Nearly 40% - 50% of newly developed and orally administered drugs exhibit solubility problem in aqueous media due to its high lipophilicity, which directly reflects in the difficulty in formulation development of those drugs. Even though oral route is the most preferred route for drug administration due to its fulfillment of necessary strategies for drug development and patient acceptance, the poorly soluble drugs generally exhibit slow dissolution rates and incomplete bioavailability due to poor wettability in the gastro intestinal tract (GIT).

Different methods are employed to improve the dissolution characteristics of poorly water soluble drugs, like solubilization, pH adjustment, co solvents, microemulsion, self emulsification, polymeric modification, drug complexation, particle size reduction, use of asurfactantas a solubilizing agent,the prodrug approach and solid solutions. Amongst these the most promising technique is liquisolid compact technique.

Liquisolid Compacts - A Novel Approach

The term ‘liquid medication’ involves oily liquid drugs and solutions o rsuspensions of water insoluble solid drugs carried in suitable non volatile solvent systems termed liquid vehicles. Employing this liquisolid technique, a liquid medication may be converted into a dry looking, non-adherent, free flowing and readily compressible powder by a simple blending with selected powder excipients referred to as carrier and coating materials. Various grades of cellulose, starch and lactose may be used as the carriers, whereas very fine particle size silica powders may be used as the coating (or covering) materials In fundamental studies made by Spireas etal., flow and compression issues have been addressed with the use of the new formulation mathematical model of liquisolid systems, which is based on the flowable (Φ-value) and compressible (Ψ - number) liquid retention potentials of the constituent powders. The good flow and compression properties of the liquisolid system are encouraged by the large surface area and fine particle size. Hence, liquisolid compacts containing water-insoluble drugs are expected to display enhanced dissolution characteristics and, consequently, improved oral bioavailability.

2. Materials and Methods

2.1) Materials:

Flunarizine HCL was received as a gift sample from Aurobindo Pharma Ltd., Hyderabad, India. Poly ethylene glycol 400, Tween 80, microcrystalline cellulose, Aerosil, Sodium Starch Glycolate, Magnesium Stearate was purchased from S.D Fine chem. LTD Mumbai.

2.2) Method

Formulation Development

Model drug was initially dispersed in the non volatile solvent systems (PEG 400 and Tween 80) termed as liquid vehicles with different drug: vehicle ratio. Then a mixture of carrier (Avicel pH 102 was added to the above liquid by Continuous mixing for a period of 10 to 20 minutes in a mortar. Then to the above mixture coating material was added and mixed thoroughly. The amount of carrier and coating materials added were based on the R value. To the above binary mixture disintegrant like SSG and other remaining additives such as Glidant (magnesium stearate) are added according to their application and mixed in a mortar.The final blend was compressed.

- **Application of New Mathematical Model for Design of Liquisolid System**

The liquisolid technique as suggested by Spireas etal, states that the drug dissolved in a liquid vehicle is incorporated into carrier and coating materials having porous structure and closely matted fibres in its interior, is a phenomenon of both adsorption and absorption.

Coating materials like Avicel PH 102 have high adsorptive capacity and greater surface area and thus gives the liquisolid systems the desirable flow and compaction properties. The quantity of carrier material (Q) required, the quantity of coating material (q), Liquid load factor (Lf) and excipients ratio (R) was calculated by using the following equations;

Amount of carrier material required (Q) = W/L_f

Amount of coating material required (q) = Q/R

Liquid load factor (L_f) = W/Q

Excipient Ratio (R) = Q/q

Table no 2.2: Formulation of Liquisolid Compacts.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Flunarazine	10	10	10	10	10	10	10	10

PEG400(w/w%)**	2.5	5.0	7.5	10				
Tween 80					2.5	5.0	7.5	10
Carrier:coating material (R)	20	20	20	20	20	20	20	20
Liquid load factor (L_f)	0.125	0.15	0.175	0.20	0.125	0.15	0.175	0.20
MCC(mg)	100	100	100	100	100	100	100	100
Aerosil(mg)	5	5	5	5	5	5	5	5
SSG(w/w)*	5	5	5	5	5	5	5	5
Lactose Anhydrous	26.5	24	21.5	19	26.5	24	21.5	19
Mg.stearate(w/w%)*	1	1	1	1	1	1	1	1
Total weight	150	150	150	150	150	150	150	150

Where W is the ratio of weight of coating material and liquid medication, L_f is the Liquidload factor, R is the carrier.

**** Drug concentration in liquid vehicle**

*** Percent in total weight of the tablet**

2.2.1) Preformulation studies

Investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rationale development of dosage form.

2.2.1.1) Drug-Excipients compatibility studies by FT-IR

In the preparation of liquisolid compact, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Flunarizine HCl and the selected polymers. The individual drug and drug with excipients were scanned separately.

2.2.1.2) Evaluation of Precompression parameters

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel Method and is the measure of the flowability of powder/granules.

$$\theta = \tan^{-1}(h/r) = \tan^{-1}(\text{height of pile}/0.5\text{base})$$

Bulk density

Apparent Bulk density (gm/ml) of the drug was determined by pouring (preseived 40-mesh) gently 4 gm of sample through a glass funnel into a 10 ml graduated cylinder. Then after pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density was calculated by following formula.

Bulk density = Weight of powder / Bulk volume

Tapped density

Tapped densities the drug was determined by pouring gently 4 gm of sample through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping were recorded and tapped density was calculated.

Tapped density = Weight of powder / Tapped volume

Compressibility index (carr's index)

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density.

Carr's index = (Tapped density – Bulk density / Tapped density) X 100

Hausner's ratio

Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value of indicates better flow and vice versa.

Hausner's Ratio = Tapped density /Bulk density

2.2.2) Evaluation of tablets

Hardness: Hardness of tablet was measured by Monsanto hardness tester. Foreach batch three tablets were tested and results are expressed in **Kg/cm^2**.

Thickness: Tabletswererandomlyselectedfromeachbatchandtheirthicknesswas measured by usingverniercalipers. It is expressed in millimeter (mm).

Friability: Friability of buccal tablet was determined using Roche friabilator. Preweighed sample of tablets (10 tablets) was placed in a friabulator and operated at 25 rpm for 4 minutes or run up to 100 revolutions after four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The percentage friability was determined by the formula:

$$\% \text{ Friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

Weight variation test

Ten tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Drug content uniformity

10 tablets were taken and powdered. Powder equivalent to one tablet was weighed accurately and allowed to dissolve in 10ml phosphate buffer and make up volume upto 100ml. The solution was filtered; 1 ml of filtrate was taken in 50 ml of volumetric flask and diluted up to mark with 6.8 phosphate buffer and analyzedspectrophotometrically at 278nm.

3. Results and Discussion

3.1 Analytical Method Development

3.1.1 Determination of λ_{max}

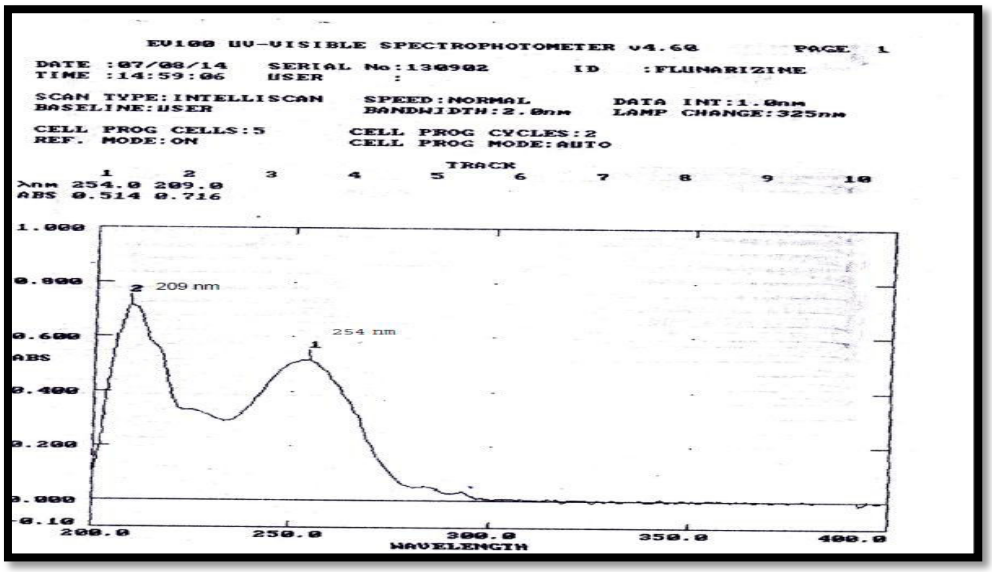

Fig .3.1.1: Graph indicating λ_{max} of FlunarizineHCl.

Discussion:

From the above graph,the maximum absorbance (λ_{max}) peak was observed at 254nm.

3.1.2 Standard Calibration Curve of Flunarizine HCL.

Table-3.1.2: Standard calibration curve for Flunarizine HCl in 0.1N HCL at 254nm.

S.no	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	4	0.25
3	6	0.43
4	8	0.59
5	10	0.72
6	12	0.87

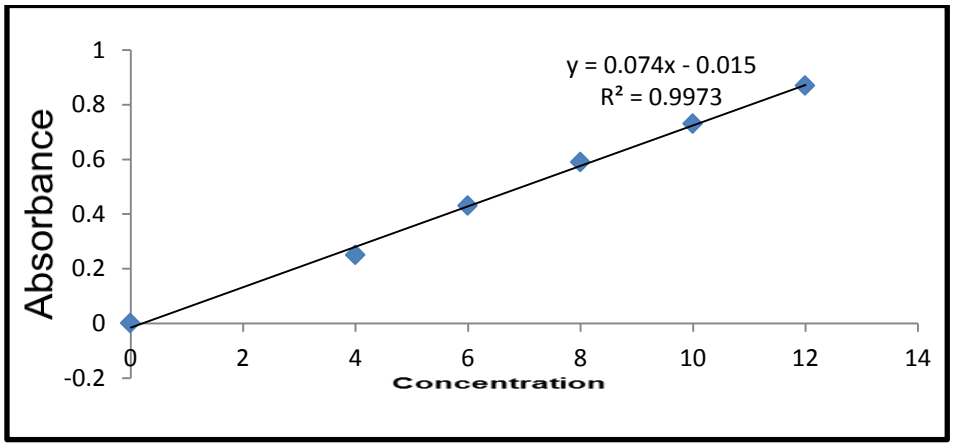

Figure no 3.1.2: Calibration graph

Discussion:

The absorbance data for standard calibration curves are given in table. The Standard calibration curve of Flunarizine HCl yields a straight line, i.e, good linearity with R^2 values 0.9973 in 0.1 N HCl which shows that the drug follows Beer's-law in the concentration range of 4-12µg/ml.

3.2 Preformulation Studies

3.2.1) Drugexcipient Compatibility Studies By FTIR

The spectrum obtained after the analysis is shown below. The spectrum of the standard and the samples were then superimposed to find out any possible interactions between the drug and the polymers. All the characteristic peaks of Flunarazine were also found in the spectrum formulations.

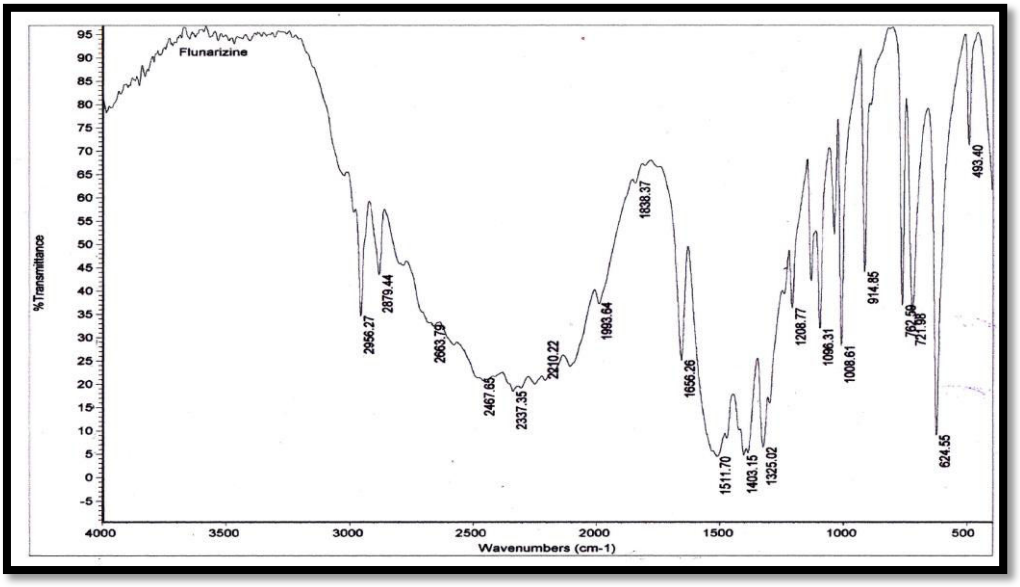

Fig 3.2.a: FTIR spectra of Flunarazine pure drug.

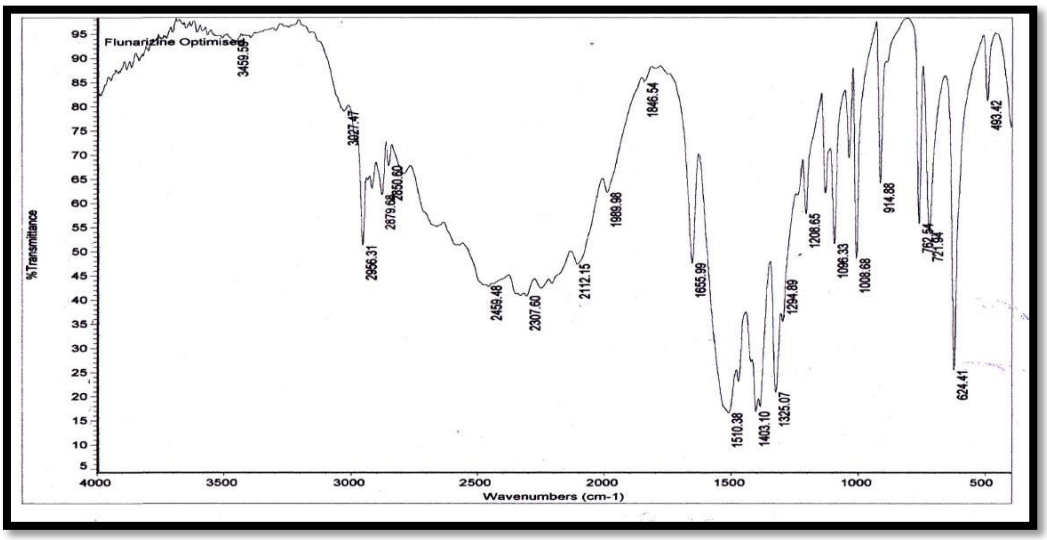

Figure no 3.2.b: FTIR spectra of Flunarazine with Tween 80.

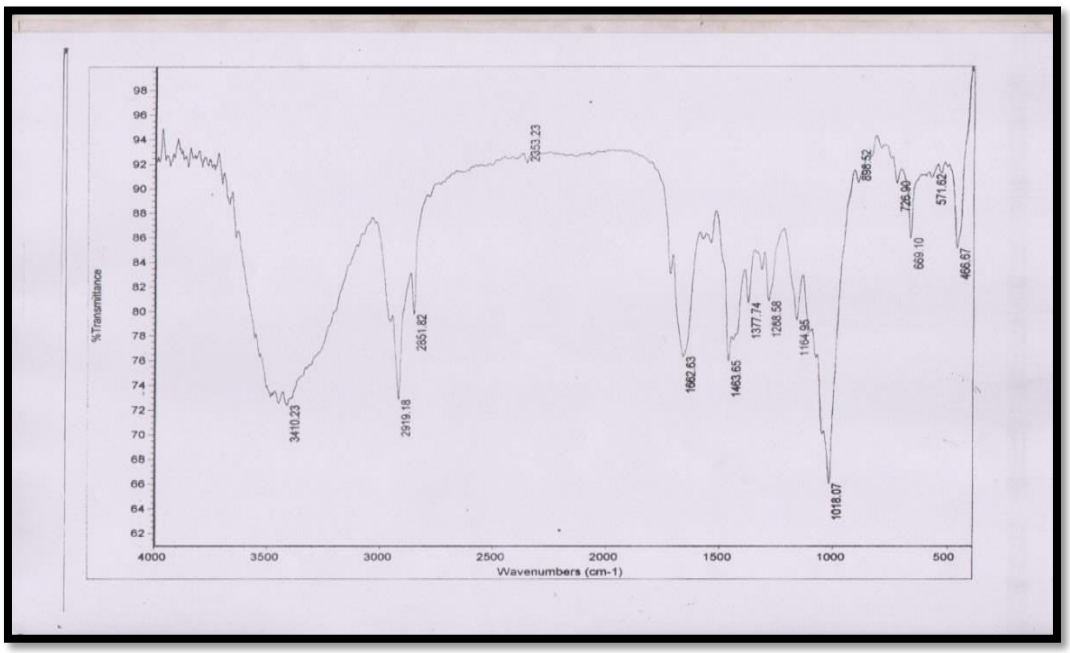

Figure no 3.2.c: FTIR spectra of Flunarazine with PEG 400.

Table no 3.2: Interpretation data of IR spectra of Flunarazine and final formulation.

Type of vibration	IR Absorption bands			
	Characteristic peak	Observed peak in pure form	Observed peak in Drug with PEG 400	Observed peak in Drug with Tween 80
C-H Bond	2960 – 2850	2956.27	2956.31	2935.57
O-F (alkyl)	1365 – 1120	1325.02	1325.07	1277.52
Aliphatic C=C Bond	995 - 985 and 940 – 900	914.85	914.85	997.86

Discussion:

A comparative study of flunarizine is done by using FTIR spectroscopy to study the compatibilities between drug and excipients. It was observed that there is no interaction between drug and excipient.

3.4 Evaluation of Pre Compression Parameters

Table no 3.3: Preformulation evaluation parameters

FORMULATION CODE	BULKDENSITY (gm/ml)	TAPPED DENSITY (gm/ml)	CARR'S INDEX (%)	HAUSNER'S RATIO	ANGLE OF REPOSE	FLOW
F1	**0.30**	**0.37**	**18.9**	**1.23**	**28.6^0**	**Good**
F2	**0.25**	**0.30**	**16.6**	**1.20**	**26.4^0**	**Good**
F3	**0.25**	**0.31**	**19.3**	**1.24**	**30.4^0**	**Good**
F4	**0.710**	**0.87**	**19.71**	**1.25**	**26.3^0**	**Good**
F5	**0.21**	**0.30**	**16.0**	**1.19**	**28.4^0**	**Good**
F6	**0.37**	**0.48**	**23.18**	**1.299**	**26.3^0**	**Good**
F7	**0.37**	**0.45**	**17.7**	**1.21**	**28.7^0**	**Good**
F8	**0.38**	**0.50**	**23.91**	**1.31**	**29.4^0**	**Good**

Discussion: The flow properties of all the powders are tested for all the formulations and it was observed that all the formulations show good flow properties. Among this. F7 is considered as optimized formulation as it is showing bulk

density of 0.37gm/mL, tapped density of 0.45gm/mL, Carr's index as 17.7%, Hausner's ratio as 1.21 and Angle of repose as 28.7^0 which is considered as good and is suitable for direct compression.

3.4 Evaluation of Post Compression Parameters.

Table 3.4: Evaluation tests for various formulations of FlunarizineHCl.

S.No	**Physical parameter**	F1	F2	F3	F 4	F 5	F 6	F7	F8
01	**Avg Weight (mg)**	**153.3**	**150.1**	**149.0**	**152.1**	**152.4**	**151.3**	**149**	**152**
02	**Hardness (kg/cm^2)**	**4.8**	**5.2**	**5.0**	**5.6**	**5.4**	**5.6**	**5.3**	**5.4**
03	**Thickness (mm)**	**3.1**	**2.11**	**2.1**	**2.11**	**2.15**	**2.15**	**2.21**	**2.31**
04	**Friability %**	**0.5**	**0.52**	**0.45**	**0.52**	**0.4**	**0.25**	**0.36**	**0.4**
05	**Disintegration Time(Secs)**	**50**	**45**	**48**	**55**	**50**	**55**	**49**	**54**
06	**% Drug Content**	**98.9**	**98.7**	**99.3**	**101.8**	**100.1**	**100.3**	**99.6**	**99.4**

Discussion: From the above table, it was found that F7 shows good hardness (5.3 Kg/cm^2)and thickness of 2.21mm. Friability is 0.36%. The disintegration time is also very less in F7 formulation. The less the disintegration time, the faster the drug will break into pieces and enhance dissolution rate.

3.5 Dissolution Profiles

Table no 3.5: Comparative Invitro Dissolution Studies.

Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**Marketed Formulation (SIBELIUM)**
10	28	35	37	26	33	35	**35**	33	**20**
20	45	48	53	39	45	44	**42**	46	**32**
30	54	56	64	46	59	56	**65**	58	**42**
40	69	68	70	58	65	68	**75**	71	**59**
50	75	77	76	65	77	78	**86**	80	**68**
60	79	82	84	74	82	85	**98**	84	**82**

90	--	--	--	--	--	--	--	--	**93**
120	--	--	--	--	--	--	--	--	**100**

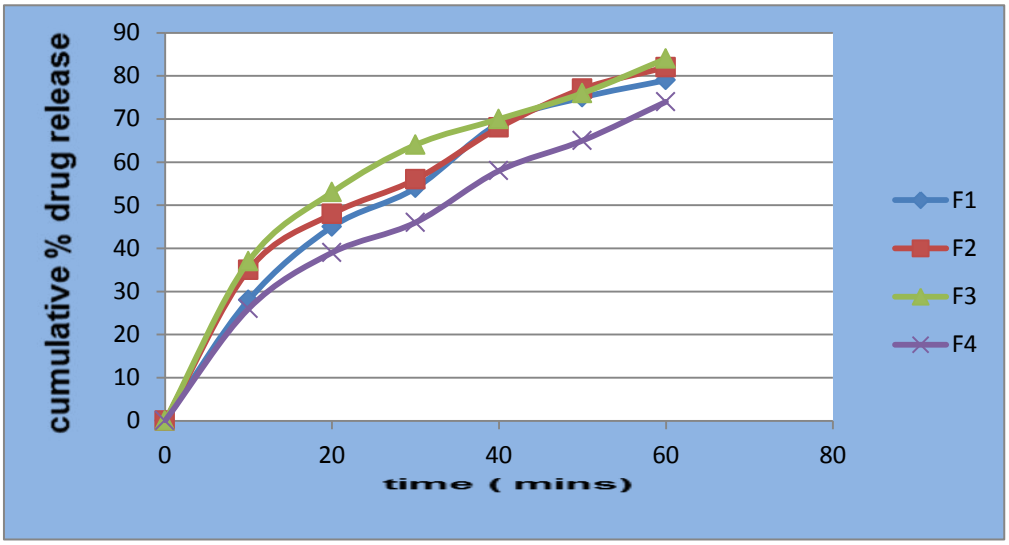

Figure No 3.5.a: Dissolution Study of Formulations F1-F4.

Discussion: Dissolution test was performed for F1-F4 formulations using PEG 400. Among these F3 shows high dissolution rate (84%).

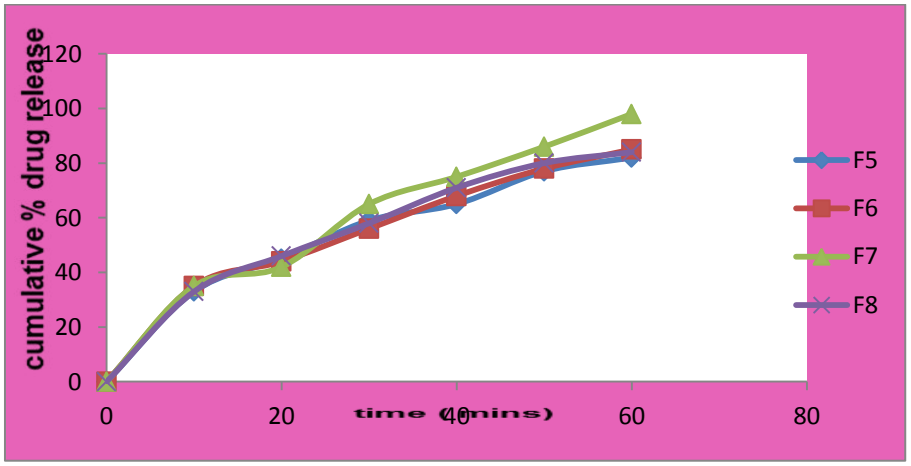

Fig no 3.5.b: Dissolution Study of Formulations F5-F8.

Discussion: Dissolution test was performed for F5-F8 formulations using TWEEN 80. Among these F7 shows high dissolution rate (98%).

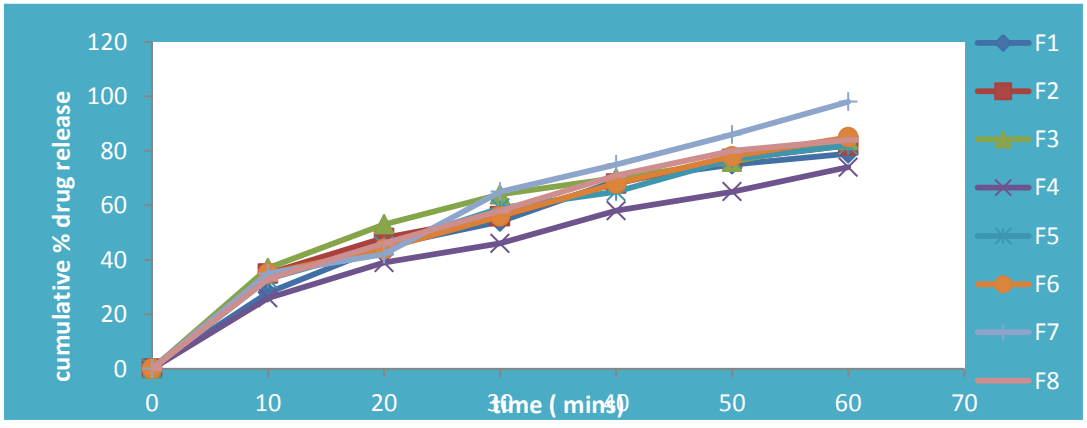

Fig no 3.5.c: Dissolution Study of Formulations F1-F8.

Discussion:

Dissolution test was performed for all the formulations. Among all the formulations of flunarizine HCl, F7 has maximum % drug release (98%). Therefore F7 is my optimized formulation.

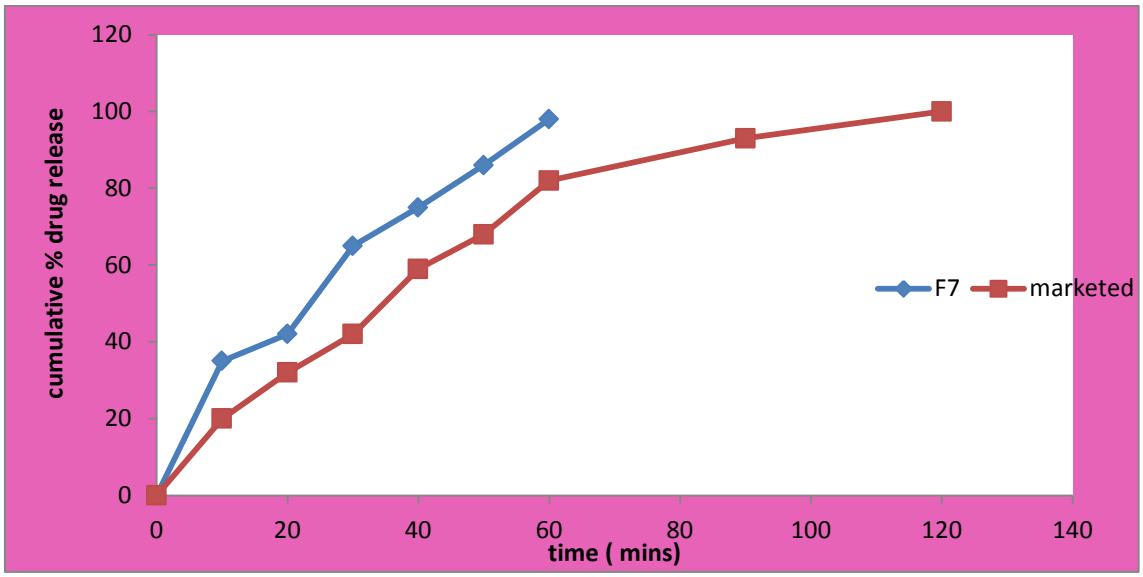

Figure no 3.5.d: Comparitive Dissolution Study of F7 Formulations With Marketed Product (SIBELIUM).

Discussion:

The comparative dissolution studies shows that optimized formulation exhibited drug release of 98% within 60 min, whereas sibelium (marketed drug) shows drug release of 100% in 2 hrs.

3.6 Drug Release Kinetics of Optimized Formulation F7:

Table-3.6: Release kinetics for the optimized formulation.

	ZERO	FIRST	HIGUCHI	PEPPAS
F7 formulation	**% CDR Vs T**	**Log % Remain Vs T**	**%CDR Vs √T**	**Log C Vs Log T**
Slope	-0.024271317	1.532142857	12.59474552	1.091754021
Intercept	2.151783416	11.32142857	-4.344386099	-0.55274894
Correlation	-0.919339317	0.978320606	0.989495914	0.65109977
R 2	0.845184781	0.957111208	0.979102164	0.423930911

Discussion:

The Dissolution data were fitted into different kinetic models like Zero-order, First order, Higuchi's model and Peppa's models. The correlation coefficient values (R^2) of optimized formulation of flunarizineHCl indicate that the drug release was following first order release kinetics and non -fickian mechanism.

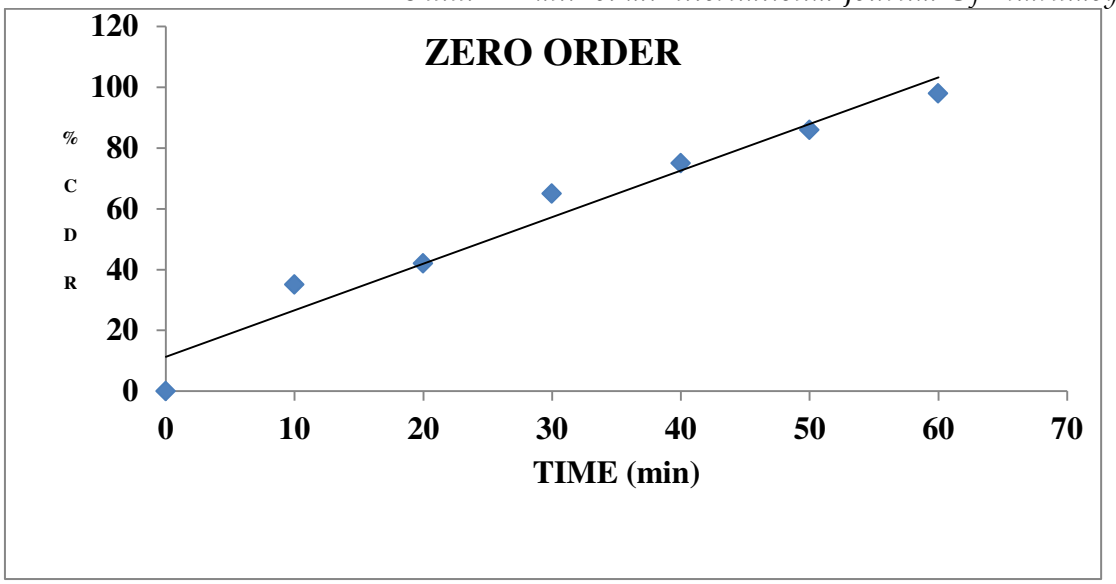

Fig 3.6.a- Zero Order release of optimized formulation.

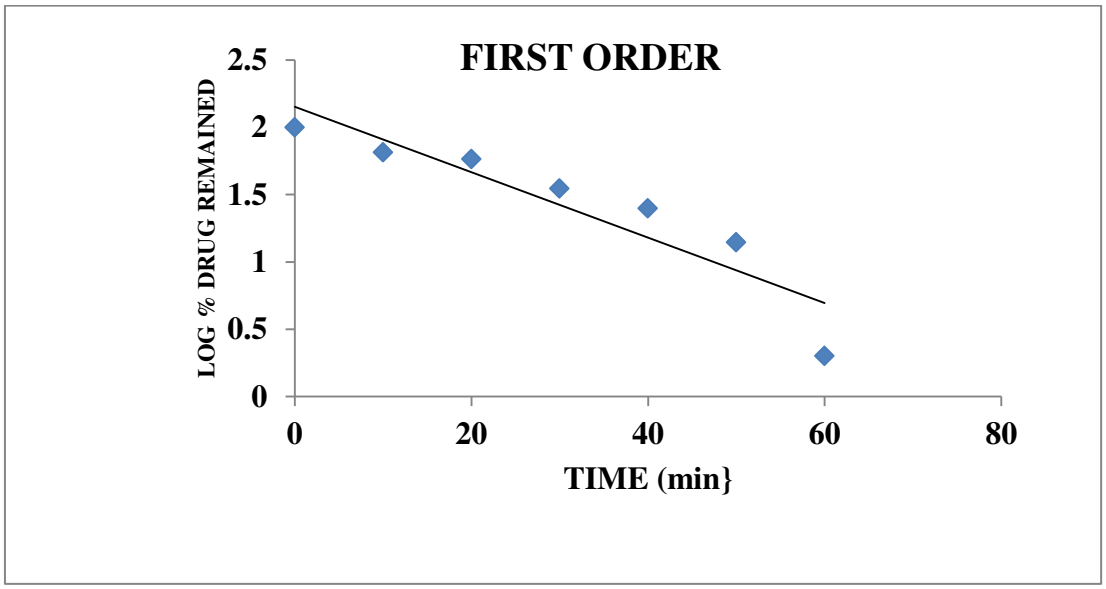

Fig 3.6.b- First Order release of optimized formulation.

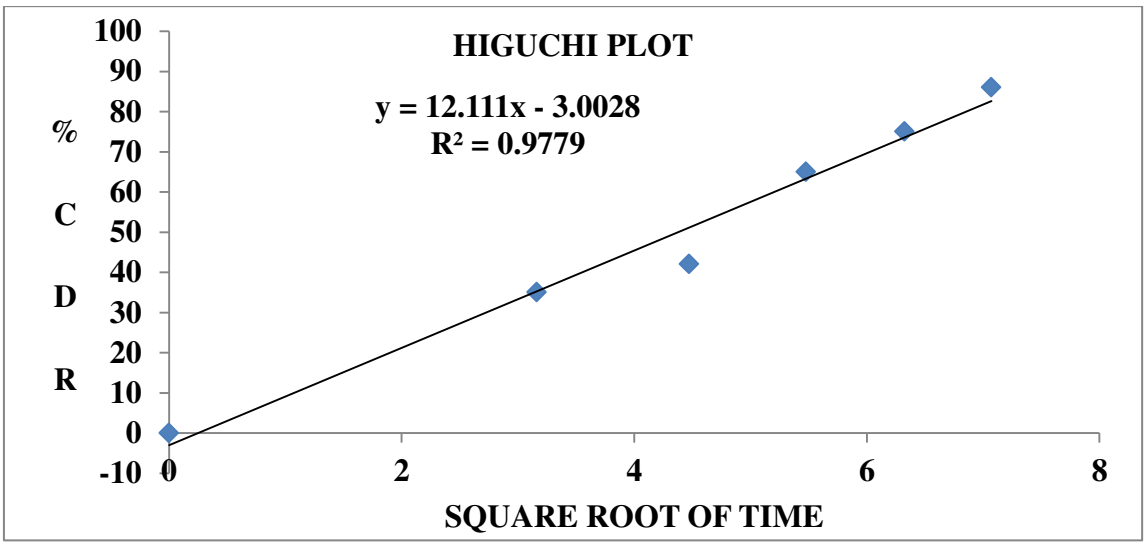

Fig 3.6.c- Higuchi plot of optimized formulation.

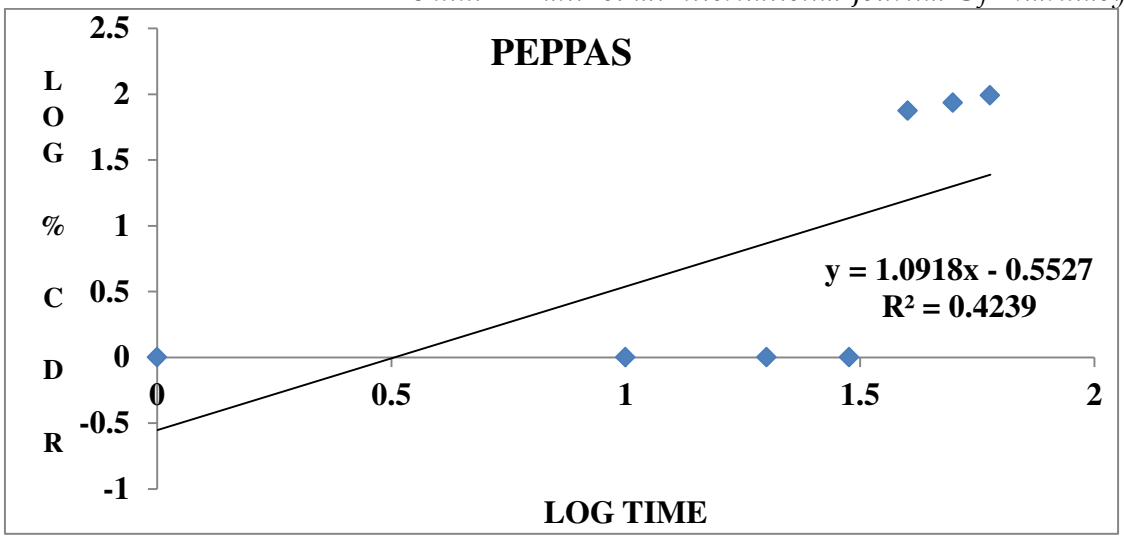

Fig 3.6.d- Peppas plot of optimized formulation.

3.7 Stability Studies

Table No 3.7: Stability data of optimized formulation of FlunarazineLiquisolid Compacts.

S.No	Time	Initial	Cumulative % Drug Release (mean ± SD) (n=3)			
			$25^{o}C/60\%RH$		$40^{0}C/75\%RH$	
			1st Month	3rd Month	1stMonth	3rdMonth
1	**60 Mins**	98	98.68	98.07	98.12	97.45
2	**Assay**	99.56± 0.59	99.01 ± 1.06	99.00 ± 0.56	98.89 ±0.19	98.37 ±0.31

Inference:

No significant change was observed in the percentage drug dissolved after storage period of 1 & 3 months at 25^{0} C/ 60% RH and 1&3 months at 40^{0}C/75% RH for Flunarazine Liquisolid compact.

4. Conclusion

From the results obtained from executed experiments it can be concluded that:

- The preformulation studies like melting point, flow properties of Flunarazine were compiled with IP standards.
- The FTIR spectra revealed that, there was no interaction between polymer and drug. Polymersused were compatible with Flunarazine.
- Among the Tween 80 in 1:3 ratio (F7) was showing best release. F7 showed increased dissolution profile.
- Stability studies showed that there were no significant changes in physical and chemical properties of tablet of formulation F7 after 3 months.

- The optimized drug (F7) showed hardness 5.3 kg/cm^2, friability 0.36% indicating good mechanical strength, % drug content was found to be 99.6%, disintegration time was 49 sec and % drug release was 98% in 60 min.
- The Dissolution data were fitted into different kinetic models like Zero-order, First order, Higuchi's model and Peppa's models. The correlation coefficient values (R^2) of optimized formulation of flunarizine HCl indicate that the drug release was following first order release kinetics and non fickian mechanism.
- No significant change was observed in the percentage drug dissolved after storage period of 1 & 3 months at 25^0 C/ 60% RH and 1&3 months at 40^{0}C/75% RH for FlunarazineLiquisolid compact
- This research work has produced encouraging results in terms of increasing the invitro dissolution of poorly soluble drugs such as Flunarazine using liquisolid technology and we expect a good correlation between the in vitro and invivo performance of the formulations.
- The technique being simple and effective can also be extended to other poorly soluble drugs.
- The invivo performance of the liquisolid compacts has to be studied using animal models to claim a complete success in the development of these formulations.

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