FORMULATION, OPTIMIZATION AND EVALUATION OF LIQUISOLID TABLETS CONTAINING TADALAFIL

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ABSTRACT:-

Objective:- The aim of our study was to improve the avaibility of Tadalafil a practically insoluble erectile dysfunction drug. As a model drug by using liquisolid technique. The effect of powder susstrate composition on the flowability and compressibility of liquisolid compacts were evaluated. Specifically, several liquisolid formulations, containing 10mg Tadalafil, which containing different carrier to coating ratios in their powder substrates and a fixed liquid medication, were prepared. The dissolution profiles of Tadalafil liquisolid tablets were determined according to USP method. The obtained dissolution profile were compared to that of a commercial product. In the present study, the formulated liquisolid systems exhibited acceptable flowability and compressibility. In addition, liquisolid tablets displayed significant enhancement of the dissolution profiles compared to this of commercial one.

Results and discussion: Prepared liquisolid tablets were evaluated for pre-compression and post-compression parameters. Angle of repose, carr's index and hausner's ratio were found to be in acceptable range. Hardness, friability, disintegration time, were found to be in specified range for all formulations. *In-vitro* drug release of liquisolid tablets were higher compared to control and marketed tablets due to its less contact angle and more wettability. Significantly improved dissolution profile was observed for all liquisolid formulation as compared to that of marketed formulation as indicated from *in-vitro* dissolution study (108.33%) which was due to presence of polyethylene glycol which increase fluid penetration in to formulations. Moreover the desirability value of various dependent variables was found to be nearer to one. Performance of optimized formulation (A1) remained consistence at the end of stability study.

KEYWORDS:- Liquisolid tablets, Tadalafil, PEG 800, Avicel pH 102, Aerosil200, PVP k30

INTRODUCTION:-

The poor dissolution rate of water insoluble drug is still a substantial problem confronting the pharmaceutical industry. The numbers of new and, beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution[1].

1.1 Liquisolid System

The technique of 'liquisolid compacts' is a new and promising addition towards such a novel aim. The term 'liquid medication' implies oily liquid drugs and solutions or suspensions of water insoluble solid drugs carried in suitable nonvolatile solvent systems termed the liquid vehicles. Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability[1].

1.2 Theoretical aspects

The flowability and compressibility of liquid of liquisolid compacts are addressed simultaneously in the 'new formulation mathematically model of liquisolid system',

excipients ratio (R) or the carrier to coating ratio of the powder system use, where,

$$R = Q/q$$

R represents the ratio between the weights of carrier (Q) and coating (q) material liquid load factor (L_f) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system.

$$L_f = W/Q$$

The powder excipients ratio R and liquid load factors L_f of the formulations are related as follows:

$$^{\Phi}L_f = \Phi + \Phi\,(1/R)$$

1.3 Classification of liquisolid system

Liquisolid techniques are categorized as per following consideration[2],

A. Based on the type of liquid medication contained in liquisolid systems:

i. Powdered drug solutions

ii. Powdered drug suspensions

iii. Powdered liquid drugs

B. Based on the formulation technique used in liquisolid systems:

i. Liquisolid compacts ii. Liquisolid microsystems

1.4 Advantages of liquisolid systems

- Increase bioavailability of poorly water soluble drugs.
- Less production cost compared to soft gelatin capsules.
- Suitable for industrial production.

1.5 Disadvantages of liquisolid system

- Liquisolid system requires low drug loading capacities
- Higher amounts of carrier and coating materials are required.

MATERIALS AND METHODS:-

1. Materials

Tadalafil (TDL), were supplied as a gift sample from Alembic Research Ltd (Vadodara, India).Polyethylene glycol (PEG-800), sodium starch glycolate (SSG), Avicel PH102, Aerosil 200 were procured from Lupin Research Park (Pune, India). Sodium Laurel Sulphate (SLS) and other raw materials were procured from S. D. Fine (Mumbai, India).

2. Equipment

Electric balance (Mettler AJ100, Switzerland), Ultraviolet spectrophotometer (Jenway 6305 uv/vis. UK), Single Punch tablet press (First Medicine machinery shanghai factory of Dongha Branch, Shanghai, China), Tablet Hardness tester (Pharmatest, Type PTB 301, Hainburg, Germany), Friability tester (Pharmatest, Type PTF1, Hainburg, Germany), Disintegration tester (Pharmatest, Type PTZ3, Hainburg, Germany), Dissolution apparatus.

3. Experimentals:-

3.1 Identification of Drug

3.1.1 By UV spectrophotoscopy

In order to ascertain the optimum wavelengths of Tadalafil, the solution of tadalafil in methanol was scanned on a UV-Visible spectrophotometer in the range of 200-400 nm against the methanol as blank and sectrum of tadalafil was recorded as shown in figure 1.1

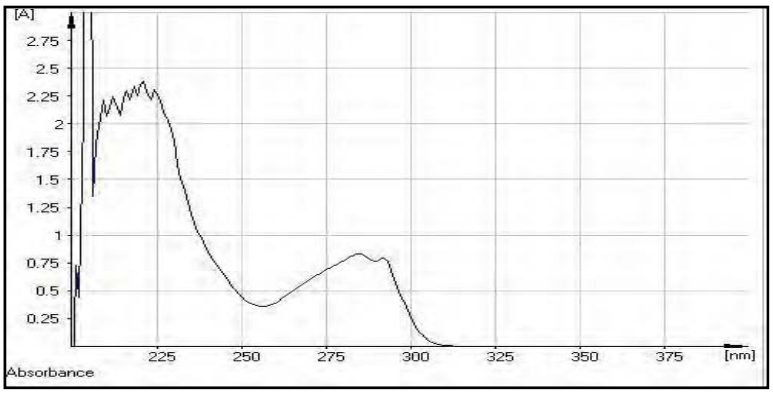


Figure 1.1: U.V. absorbance of Tadalafil in methanol.

3.1.2 By melting point determination

Open capillary method was used to determine melting point of drug as per pharmacopeia. In this methodology, a thin glass capillary tube containing a compact colum of the substance to be determined is introduced into a heated stand (liquid bath or metal block) in close proximity to a high accuracy thermometer. The temperature in the heating stand is ramped at user-programmable fixed rate until the sample in the tube transitions into the liquid state. Melting point was found to be 302^{o} C.

3.1.3 By fourier transform infrared spectroscopy analysis

Identification of Tadalafil was done by FT-IR spectroscopy. The sample was analysed by FTIR instrument (Bruker, Parul Institute of Pharmacy) and scan was recorded. The obtained IR spectrum is shown in Figure 1.2.

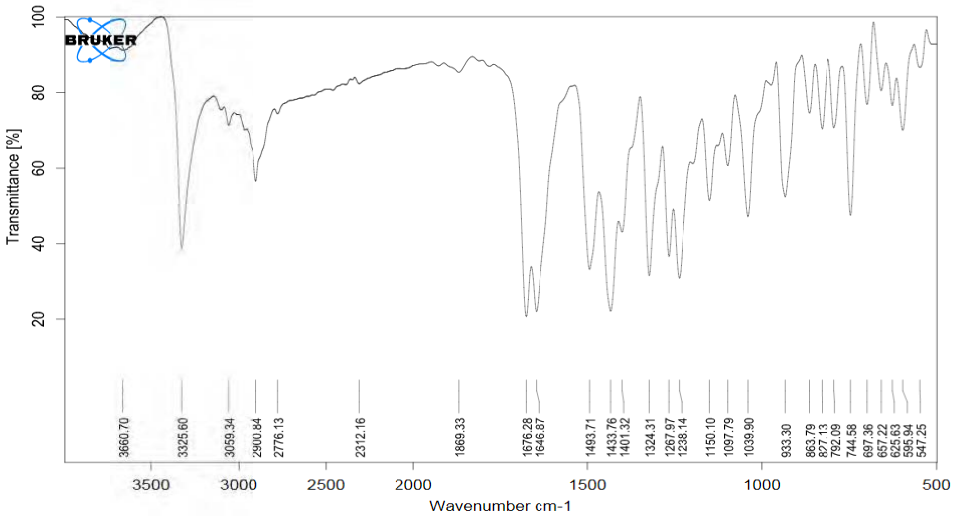


Figure 1.2: IR spectrum of pure Tadalafil powder

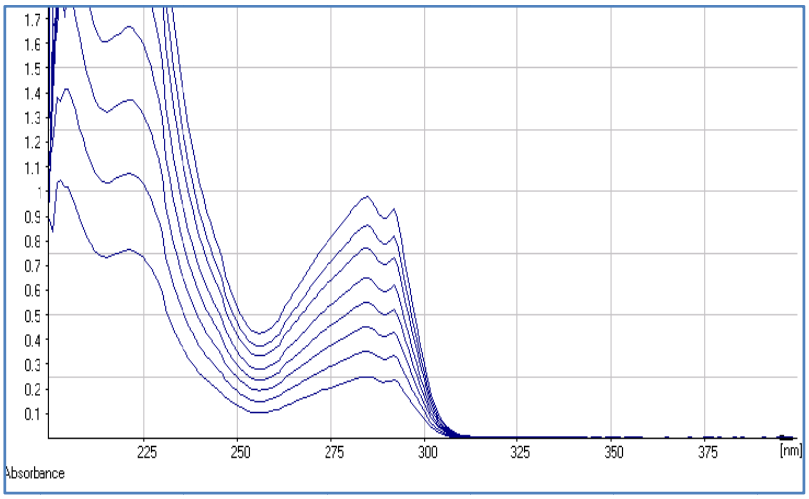
3.2 Preparation of standard calibration curve of Tadalafil

Preparation of stock solution

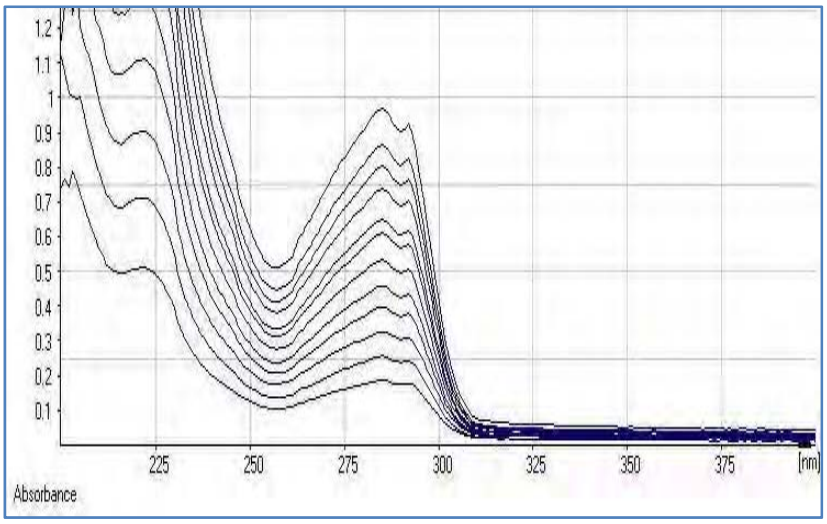
Two separate stock solution of tadalafil was prepared one by dissolving 50 mg of tadalafil into 50 ml volumetric flask containing methanol and second by dissolving 10 mg of tadalafil into 100 ml volumetric flask containing 0.5% Sodium lauryl sulphate.

Procedure

Aliquots (0.3 to 2.7 ml) of above prepared stock solution were transferred into series of 10 ml volumetric flask and diluted with their respective solvents i.e. methanol and 0.5% Sodium lauryl suphate to get concentration of tadalafil in range of 3 to 19 µg/ml in methanl and 3 to 27 µg/ml in 0.5% Sodium lauryl sulphate respectively. The resulting solution were analysed at 285 nm for their absorbance against their respective blank in UV spectrophotometer. The standard calibration curve in both solvent were plotted by taking their respective absorbance on Y axis and concentration on X axis and it were further used for estimation of tadalafil. The overlain UV spectra of tadalafil in methanol and 0.5% Sodium lauryl sulphate are shown in Figure 1.3.

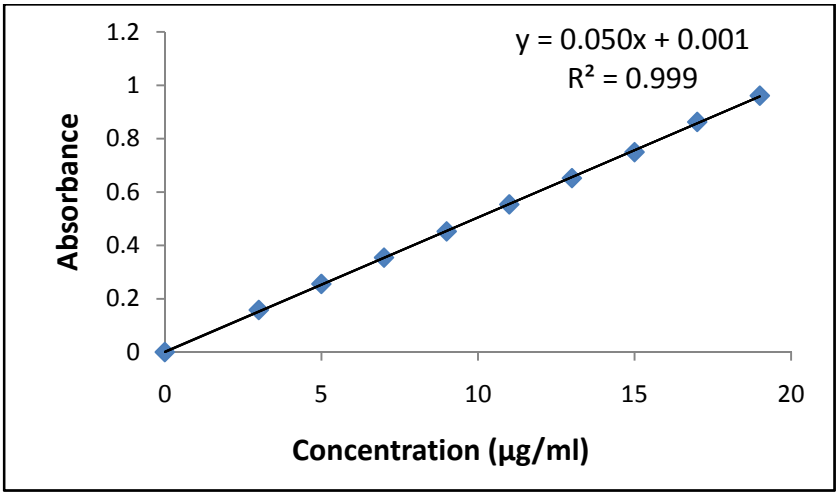


(a)

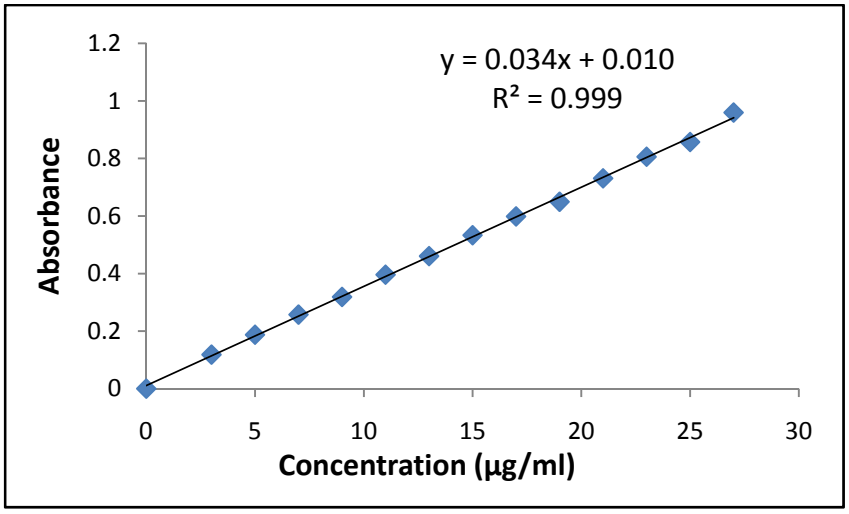


(b)

Figure 1.3 Overlain UV spectra of tadalafil in (a) methanol at concentration of 3-19 µg/ml and (b) 0.5% Sodium lauryl sulphate at concentration 3-27 µg/ml at 285 nm.



(a) methanol at concentration of 3-19 µg/ml



(b) 0.5% Sodium lauryl sulphate at concentration 3-27 µg/ml

3.3 Solubility study

The solubility of Tadalafil in various non-volatile liquid like Propylene glycol (PG), Polyethylene glycol 200 (PEG 200), PEG 400, PEG 600, PEG 800, Cremophor RH 40, Cremophor EL, Tween 20, Span 80, and Tween 40 etc. were performed for the development of liquisolid tablets. Excess amount of Tadalafil is was stirred in 2 ml of each of the selected vehicle and was shaken at 25°C for 48 hr. Supernatants were further diluted with methanol and analyzed spectrophotometrically at 285 nm for drug solubility[3]. From these results, the solubility of Tadalafil in the respective liquid vehicle was calculated.

3.4 Determination of optimal flowable liquid-retention potential (Ø -value) and liquid load factor (Lf) determination for carrier and coating materials.

Powder admixture containing 5 gm of either carrier or coating with increasing quantity of non-volatile liquid vehicle (PEG 800) were mixed using a mortar and pestle. Each admixture was then placed on a shiny metal plate, the plate was then titled till the admixture slides. The angle formed between the plate and the horizontal surface, at which admixture slides were measured as angle of slide[5] (Φ).

3.4.1 Liquid-retention potential (Ø -value)

In constant weight of carrier/coating material, increasing amount of solvent was incorporated and on each addition, angle of slide was determined. The flowable liquid

retention potential (Ø -value) of each liquid/powder admixture was calculated using the following equation.

Ø value = weight of liquid/weight of solid ---------- (1)

The Ø -values was plotted against the corresponding angle of slide (for optimal flow properties). Corresponding to 33^{o} of a liquid/powder admixture represente the flowable liquid-retention potential.

3.4.2 Determination of liquid load factors (Lf)

Appropriate amounts of carrier and coating materials were used to produce acceptable flowing and compactible powders which were be calculated using following equation.

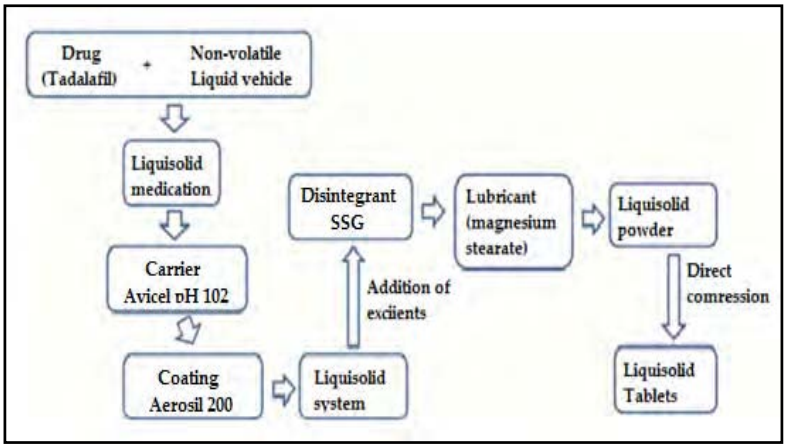
$$\mathbf{Lf} = Ø_{CA} + Ø_{CO}\,(1/R) \qquad \text{---------- (2)}$$

Where, $Ø_{ca}$ and $Ø_{co}$ value of carrier and coating material.

The maximum amount of liquid loads on the carrier material, termed ‘‘load factor” (L_f).

3.4 Method of preparation of liquisolid tablets

Several liquisolid tablets were prepared by direct compression method. Tadalafil was dissolved in PEG 800 at different ratio to obtain various drug concentration. Then a binary mixture of carrier-coating material (avicel pH 102 as the carrier powder and aerosil 200 as the coating material) was added to the obtained liquid medication under continous mixing in a motor. Depending upon the amount of carrier in formulation, different liquid loading factor were employed in liquisolid preparations. Finally, 5% (w/w) of sodium starch glycolate as the disintegrant, 5% (w/w) binder and 1% magnesium stearate were mixed with the mixture for a period of 10 min[4]. The final mixture was compressed using the rotary tablet punching machine to achieve tablet hardness.



3.6 In-vitro release of Tadalafil from liquisolid tablets:-

The *in-vitro* drug release studies was performed with USP type II paddle apparatus using 1000 ml of 0.5% sodium lauryl sulfate with paddle rotation mentioned at 37°c ± 0.5°c at 50 rpm. Samples of 5ml were withdrawn at regular time intervals 5, 10, 15, 30, 45, and 60 minutes obtained samples were filtered using whatman filter paper and resulting samples was analyzed for absorbance at 284 nm by UV visible

spectrophotometer (UV-1800, Shimadzu, Japan). The spectrophotometric readings were converted into cumulative percent of drug released using the standard calibration curve of Tadalfil previously constructed.

RESULTS AND DISCUSSION:-

1. Solubility Study:-

The solubility of tadalafil in different non-volatile liquid vehicles namely PEG 200, PEG 400, PEG 600 PEG 800, PG, Cremophor RH 40, Cremophor RH 40, Cremophor EL, Tween 20, Span 80, and Tween 40 were determined and shown in Tablet 1.1.

Table 1.1 : Solubility study of tadalafil in various non-volatile solvent (n=3)

Non-volatile liquid	Solubility (mg/ml)	Non-volatile liquid	Solubility (mg/ml)
PEG 800	**112.96 ± 0.19**	Tween 20	14.91 ± 0.11
Cremophor RH 40	85.612 ± 0.13	Span 80	6.134 ± 0.19
PEG 600	72.23 ± 0.11	Tween 40	6.57 ± 0.29
PEG 400	56.49 ± 0.21	Span 20	5.032 ± 0.31
Cremophor EL	47.41 ± 0.32	PG	1.307 ± 0.28
PEG 200	15.98 ± 0.26		

Result of saturated solubility study of tadalafil in various non-volatile liquid showed the higher solubility of tadalafil in PEG 800, followed by cremophor RH 40. It was decided to use PEG 800 as non-volatile liquid in the preparation of liquisolid tablets containing tadalafil.

2. Liquid retention potential of carrier and coating material in PEG 800

Powder admixture containing carrier and coating material with increasing quantity of PEG 800 were mixed using mortar and pestle and angle of slide was determined. Liquid retention potential of various carrier and coating material in PEG 800 were shown in Tablet 1.4, and 1.5

Table 1.4: Result of liquid retention potential (Φ-value) of various carrier material (Avicel pH101, Avicel pH 102, Avicel pH 200) in PEG 800 (n=6)

Avicel pH 101		Avicel pH 102		Avicel pH 200	
Θ	Φ-value	Θ	Φ-value	Θ	Φ-value
31.4 ± 0.12	0.11	28.73 ± 0.16	0.11	**33.8 ± 0.14**	**0.11**
33.25 ± 0.15	**0.22**	30.84 ± 0.12	0.22	32.91 ± 0.17	0.22
32.12 ± 0.11	0.34	**33.09 ± 0.11**	**0.34**	31.83 ± 0.12	0.34
31.35 ± 0.18	0.45	31.98 ± 0.17	0.45	30.45 ± 0.15	0.45
30.01 ± o.13	0.55	31.5 ± 0.19	0.55	29.07 ± 0.13	0.55

Where, θ= Angle of slide; Φ value= liquid retention potential.

Table 1.5: Result of liquid retention potential (Φ-value) of various coating material (Aerosil, Aerosil 200, Silicone dioxide) in PEG 800 (n=6)

Aerosil		Aerosil 200		Sillicone dioxide	
Θ	Φ-value	Θ	Φ-value	Θ	Φ-value
28 ± 0.18	0.225	27 ± 0.15	0.225	31.2 ± 0.11	0.045
31 ± 0.13	0.45	29 ± 0.18	0.45	**33.05 ± 0.16**	**0.09**
33 ± 0.19	**0.675**	31 ± 0.11	0.675	32.7 ± 0.18	0.135
32 ± 0.13	0.9	**33 ± 0.13**	**0.9**	31.42 ± 0.12	0.18
32 ± 0.17	1.125	31 ± 0.16	1.125	30.21 ± 0.14	0.225
32 ± 0.12	1.35	30 ± 0.12	1.35	29.08 ± 0.17	0.27

Where, θ= Angle of slide; Φ value= liquid retention potential.

From the above results, angle of slide of carrier material avicel pH 102 showed highest liquid retention potential and coating material Aerosil 200 showed highest liquid retention potential due to its more surface area compared to other carrier and coating materials which is shown Figure 1.4

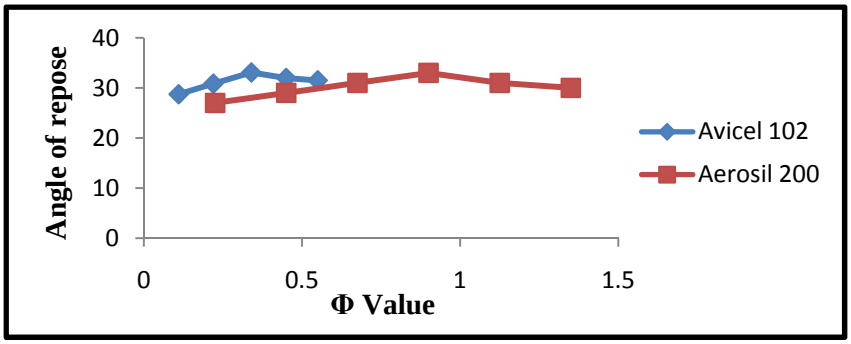


Figure 1.4: Comparision of Φ value of carrier and coating materials in PEG 800.

3. Determination of liquid load factors (Lf)

From the above result, avicel pH 102 and aerosil 200 were selected as carrier and coating material due to their high liquid retention potential.

Table 1.6: Result of liquid load factor.

R	L_f
10	0.43
20	0.38
30	0.37

Where R= Ratio of carrier to coating ratio; L_f= Liquid load factor.

From above result, it can be concluded that liquid load factor increase with decreasing carrier to coating ratio (R).

4. Method of preparation of liquisolid tablets:-

Table 1.7: Formulation of Liquisolid tablets according to 3^2 full factorial design.

Batch no	Drug con in PEG800 (%w/w)	Drug (mg)	PEG 800 (mg)	Q:q (R)	L_f	Q (mg)	q (mg)	SSG (mg)	PVP (mg)	Mag. Stear. (mg)	Total (mg)
F1	10%	10	100	10	0.43	255.5	25.5	19.5	20.5	4.30	434.8
F2	12%	10	83.3	10	0.43	217.0	21.7	16.6	17.4	3.66	369.6
F3	14%	10	71.4	10	0.43	189.3	18.9	14.4	15.1	3.19	322.4
F4	10%	10	100	15	0.4	275.0	18.3	20.1	21.1	4.64	449.3
F5	12%	10	83.3	15	0.4	233.3	15.7	17.1	17.6	3.76	380.9
F5	14%	10	71.4	15	0.4	203.3	13.5	14.9	15.5	3.28	332.0
F7	10%	10	100	20	0.38	285.0	14.2	20.8	21.5	4.51	456.1
F8	12%	10	83.3	20	0.38	242.4	12.1	17.3	18.2	3.65	387.1
F9	14%	10	71.4	20	0.38	211.4	10.5	15.1	15.9	3.34	337.8

All formulation contain 5% PVP K30, 5% SSG sodium starch glycolate, 1% mag.stearate; Q= carrier material(Avicel pH 102); q= coating material(Aerosil 200); L_f= liquid load factor; PEG= poly ethylene glycol.

4.1 Pre-Compression parameters of factorial batches

The prepared liquisolid tablets were prepared by direct compression and were evaluated for pre-compression parameters as shown in Table 1.8.

Table 1.8: Results of Pre-compression parameters of factorial batches (n=3).

Batch no	Bulk density (g/ml) ± SD	Tapped density (g/ml) ± SD	Angle of repose (θ) ± SD	Carr's index (%) ± SD	Hausner's ratio ± SD
F1	0.27 ± 0.20	0.34 ± 0.28	31.23 ± 0.28	20.88 ± 0.18	1.25 ± 0.12
F2	0.25 ± 0.24	0.30 ± 0.13	30.19 ± 0.12	17.21 ± 0.19	1.20 ± 0.22
F3	0.27 ± 0.12	0.36 ± 0.21	33.11 ± 0.26	25.00 ± 0.18	1.33 ± 0.19
F4	0.26 ± 0.28	0.32 ± 0.17	28.27 ± 0.21	18.75 ± 0.14	1.23 ± 0.22
F5	0.26 ± 0.25	0.30 ± 0.12	31.18 ± 0.23	13.00 ± 0.19	1.15 ± 0.23
F6	0.25 ± 0.12	0.33 ± 0.23	32.2 ± 0.13	24.24 ± 0.17	1.32 ± 0.11
F7	0.27 ± 0.29	0.35 ± 0.24	29.5 ± 0.21	22.85 ± 0.13	1.29 ± 0.19
F8	0.28 ± 0.21	0.32 ± 0.27	32.5 ± 0.29	12.5 ± 0.11	1.14 ± 0.22
F9	0.27 ± 0.15	0.32 ± 0.23	33.2 ± 0.17	15.6 ± 0.17	1.18 ± 0.17

4.2 Evaluation of Post-Compression parameters of factorial batches

All compressed tablets of factorial batches were evaluated for post-comprsession parameters as reported in Table 1.9.

Table 1.9: Results of post-compresssion parameters of factorial batches (n=3).

Batch	Wt. variation ± SD	Hardness (kg/cm^2) ± SD	Friability (%) ± SD	Diameter (mm) ± SD	Thickness (mm) ± SD
F1	434 ± 0.04	3.2 ± 0.22	0.30 ± 0.21	9.03 ± 0.08	6.1 ± 0.12
F2	370 ± 0.03	3.5 ± 0.19	0.54 ± 0.17	9.08 ± 0.05	5.3 ± 0.05
F3	322 ± 0.05	3.8 ± 0.25	0.56 ± 0.25	9.00 ± 0.06	4.8 ± 0.18
F4	448 ± 0.09	4.4 ± 0.18	0.26 ± 0.20	9.02 ± 0.09	6.0 ± 0.19
F5	381 ± 0.06	4.3 ± 0.21	0.33 ± 0.23	9.04 ± 0.03	5.1 ± 0.11
F6	331 ± 0.08	4.2 ± 0.25	0.24 ±0.26	9.07 ± 0.18	4.6 ± 0.08
F7	456 ± 0.04	5.2 ± 0.16	0.24 ± 0.12	9.00 ± 0.04	6.1± 0.13
F8	387 ± 0.05	4.6 ± 0.23	0.21 ± 0.18	9.06 ± 0.13	5.1 ± 0.05
F9	337 ± 0.07	4.3 ± 0.11	0.23 ± 0.11	9.01 ± 0.11	4.9 ± 0.18

Post compression evaluation tests were used to characterize liquisolid tablets. Compressed tablets were of cylindrical shape and flat faced on both sides. Diameter and thickness of each formulation batch were different due to difference in composition of each batch.

Table 1.10: Results of post-compresssion parameters of factorial batches (n=3).

Batch	Disintegration Time (min) ± S.D	Drug content (%) ± S.D
F1	1.30 ± 0.12	108.18 ± 0.28
F2	1.50 ± 0.23	95.00 ± 0.17
F3	2.0 ± 0.19	97.00 ± 0.21
F4	4.0 ± 0.26	101.0 ± 0.15
F5	2.33 ± 0.13	98.52 ± 0.11
F6	2.30 ± 0.24	100.00 ± 0.22
F7	7.05 ± 0.11	101.00 ± 0.18
F8	5.12 ± 0.18	98.00 ± 0.25
F9	3.08 ± 0.12	100.00 ± 0.17

5. In-vitro release of Tadalafil from liquisolid tablets:-

In-vitro dissolution study was performed using USP type II apparatus paddle apparatus using 900 ml of 0.5% SLS with paddle rotation of 50 rpm at 37°c ± 0.5°c.

From the different drug release profile of all the formulation, F1 gave fast release as compared to all formulations. From above table it can be concluded that all liquisolid formulations showed higher drug release compared to marketed and control formulation.

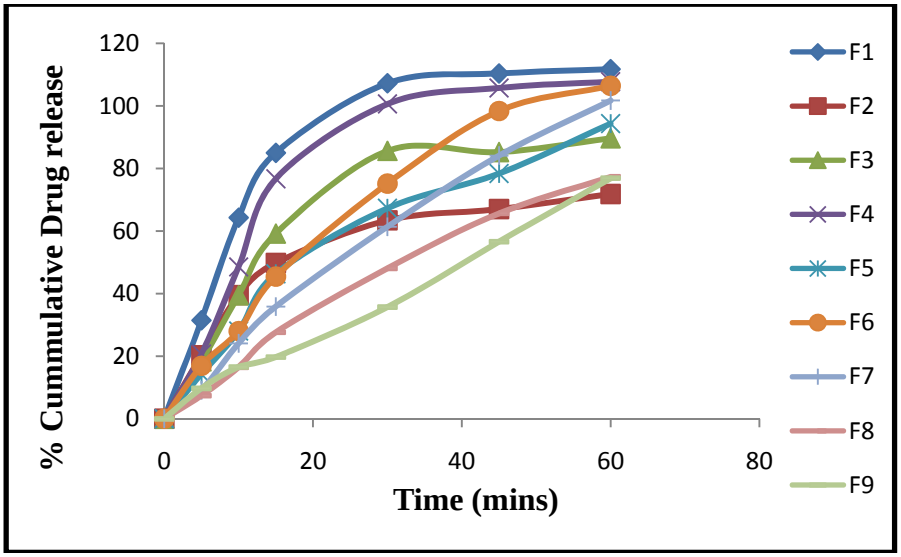


Figure 1.5: In-vitro drug release profile of Tadalafil from factorial batches.

6. Checkpoint batch compared with marketed product of Tadalafil.

The evaluation study of checkpoint batch (A1) was carried out under same condition as outlined for other batches and it was compared with marketed product of Tadalafil. % Bias was found to be within acceptable range. Result of check point batch and marketed product are shown in figure 1.6.

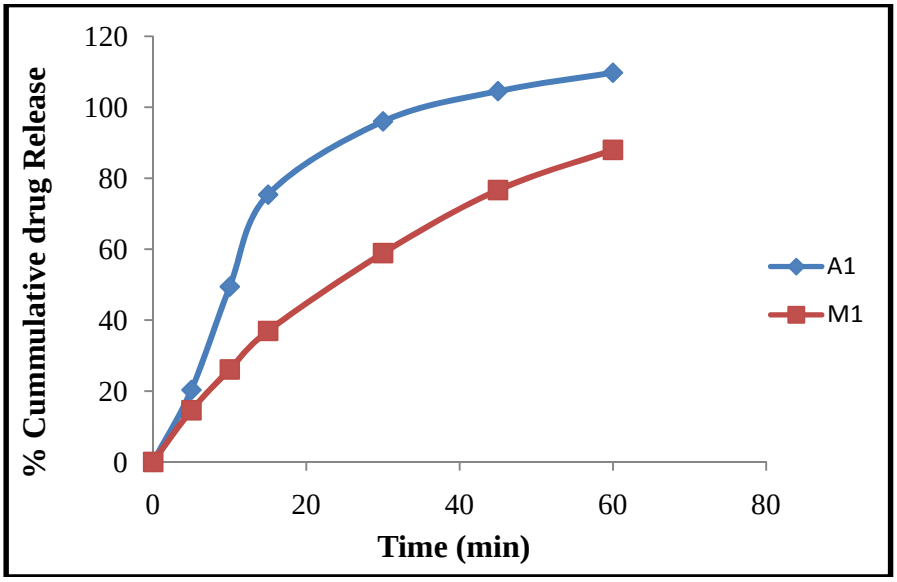


Figure 1.6: In-vitro release profile of check point (A1) with marketed tablet (M1).

7. Accelerated stability study

The stability study was performed in accordance to ICH guideline. The samples were analysed for various evaluating parameters before and after stability study. The results showed good similarity with that of before evaluated parameters[6].

Table 1.11: Comparison of evaluation parameter of optimized batch A1 before and after stability study.

Parameter	Before	After
Hardness (kg/cm^2) (Y_1)	4.4	4.2
Disintegration (min) (Y_2)	4.16	4.10
Q_5 (min) (Y_3)	20.69	19.13
T_{50}% (Y_4)	10.17	10.29
% Dissolution efficiency (Y_5)	86.76	86.17

There was no significant change in hardness, disintegration time, Q5, T_{50}% and % dissolution efficiency of optimized batch A1 after stability study.

8. Differential scanning calorimetry of drug and formulation

DSC thermograms of pure Tadalafil and other excipients in Figure 1.7, 1.8 indicated qualitative information about the physical mixture. Pure Tadalafil in Figure 1.7 shows a sharp characteristic endothermic peak at 303.40^{o}C, is agreeing with its melting temperature (Tm) and denoting that Tadalafil is in crystalline state. The liquisolid formulation in Figure 1.8 showed absence of endothermic peak. The disappearance of characteristics peaks of Tadalafil, correspond with formulation of the drug solution in the liquisolid physical mixture due to the fact that the drug is in a dissolved molecular state. Such disappearance of the drug peak upon the formulation of the liquisolid system is indicative of complete formulation of an amorphous solid solution.

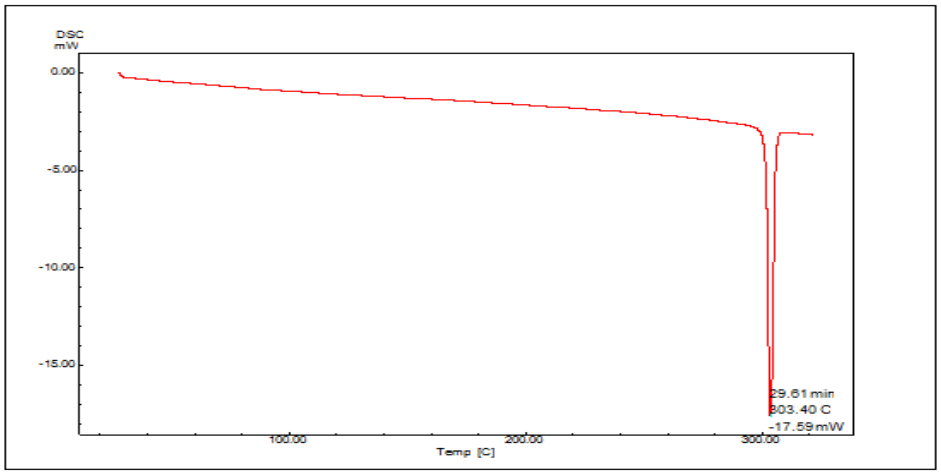


Figure 1.7: DSC thermogram of A1 containing Tadalafil

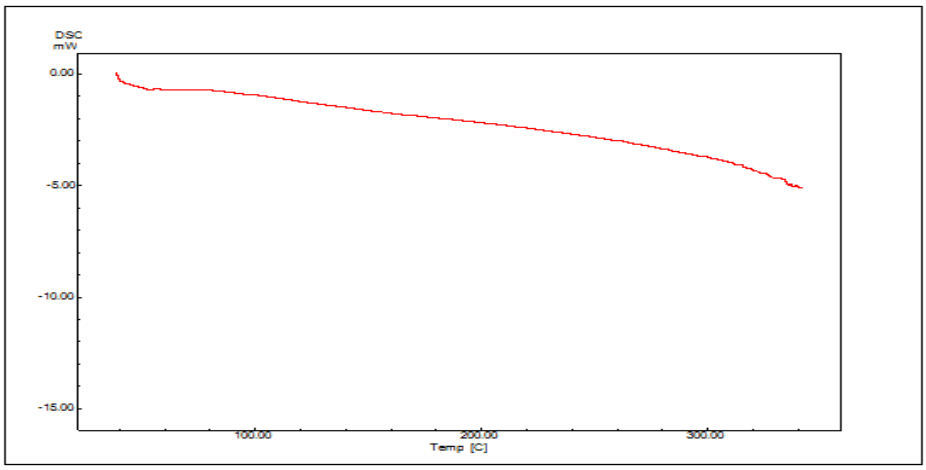


Figure 1.8: DCS thermogram of A1 containing Tadalafil and excipients.

CONCLUSION:-

In conclusion, liquisolid tablets of Tadalafil could be formulated using PEG 800 as non volatile solvent, avicel pH 102 as carrier and aerosil 200 as coating material by direct compression method. The proposed design may be used as an erectile dysfunction ensuring more effective therapy, but additional pharmacokinetic study may be required to its use in human.

Liquisolid technique was proved to be an effective method for solubility enhancement and improving dissolution profile of poorly soluble drug Tadalafil. Appropriate selection of liquid vehicle was a critical step to ensure the overall stability of API and formulation since it affects composition of liquisolid formulation which ultimately influence pre-compression and post-compression parameters.

Manufacture of liquisolid tablets seems to be exhaustive and multi-step process. Factorial design based experiments were effectively run and some statistical parameters obtained with software programme which were utilized for analyzing crucial effects. Liquisolid tablets of Tadalafil were far better in performance than the marketed product.

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