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ENHANCEMENT OF SOLUBILITY OF EFAVIRENZ BY LIQUISOLID COMPACT TECHNIQUE

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Abstract

The aim of the work was to improve the dissolution properties of the poorly soluble drug, Efaverinz by the liquisolid compaction technique. The study demonstrated with confidence that the liquisolid technique is promising approach for improvement of solubility of poorly soluble drugs. In vitro drug release of Efaverinz compacts showed increase in dissolution rate of Efaverinz. So PEG 400, PG, Tween 80 could be economic substitute as dissolution enhancing agent. Stability studies showed that there were no significant changes in physical and chemical properties of formulation F5 after 2 months. Propylene glycol in 1:0.25 ratios (F5) was showing best release. F5 was compared with marketed and prepared conventional formulation and result shows better dissolution profile.

Key words: Nifedipine, Liquisolid Compact, PEG 400, Solubility.

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INTRODUCTION

Solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. [1] The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs.

The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and, which determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract. Thus, bioavailability of poorly water-soluble drugs is limited by their solubility and dissolution rate.

Approaches for enhancement of solubility:

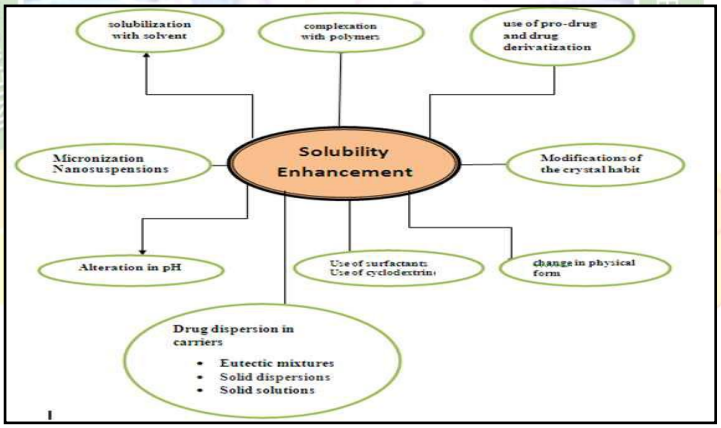

Fig. no. 1: Summarizes the various formulation and chemical approaches that can be taken to improve the solubility or to increase the available surface area for dissolutio

Liquisolid Technique:

The poor dissolution rate of water insoluble drugs is still a substantial problem confronting the pharmaceutical industry. A great number of new and possibly, beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution.

Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success.

Liquisolid technique is the one of the most promising technique of Molecular encapsulation with cyclodextrins for promoting dissolution rate of poorly water-soluble drugs. [2, 3] Low cost, simple formulation technique and capability of industrial production serve to be advantages of this technique.

The term liquisolid compacts as described by Spireas et.al indicates that immediate or sustained release tablets or capsules that are prepared using the technique of "liquisolid systems" combined with inclusion of appropriate adjuvants required for tabletting or encapsulation such as lubricants and for rapid or sustained release action, such as disintegrants or binders, respectively. Liquisolid compacts prepared by using different solvents which dissolves the poorly soluble drug and gives better bioavailability. It has been observed that the drug release superiority of liquisolid tablets is inversely proportional to the aqueous solubility of the contained drug. [4]

Liquisolid system [5, 6] involves conversion of liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent and this liquid medication can be converted into free-flowing, non adherent, dry looking, and readily compressible powders with the use of carrier and coating materials. In case of water soluble drugs, the sustained release can be obtained. "liquisolid systems" is formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water-insoluble solid drugs in suitable non-volatile solvent systems, into "dry" (i.e., dry-looking), nonadherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

Based on the type of liquid medication contained therein, liquisolid systems may be classified into three subgroups:

- Powdered drug solution
- Powdered drug suspensions
- Powdered liquid drugs.

The first two may be produced from the conversion of drug solutions or drug suspensions and the

latter from the formulation of liquid drugs into liquisolid system. [7]

Based on the formulation technique used, liquisolid systems may be classified into two categories, namely,

- liquisolid compacts : The liquisolid are prepared using the previously outlined method to produce tablets or capsules.
- liquisolid microsystems are based on a new concept which employs similarmethodology combined with the inclusion of an additive, e.g., polyvinylpyrrolidone (PVP), in the liquid medication which is incorporated into the carrier and coating materials to produce an acceptably flowing admixture for encapsulation.

The advantage stemming from this new technique is that the resulting unit size of liquisolid microsystems may be as much as five times less than that of liquisolid compacts.

Applications of liquisolid systems:

- Solubility and dissolution enhancement.
- Used efficiently for water insoluble solid drugs or liquid lipophilic drugs **(Spireas S et al., 1999 & Spireas S et al., 2002). [**8,5]
- Designed for controlled release tablets such as for rapid release, sustained release of water soluble drugs such as Propronolol hydrochloride etc.
- Application in probiotics.

Preparation of liquisolid compacts:

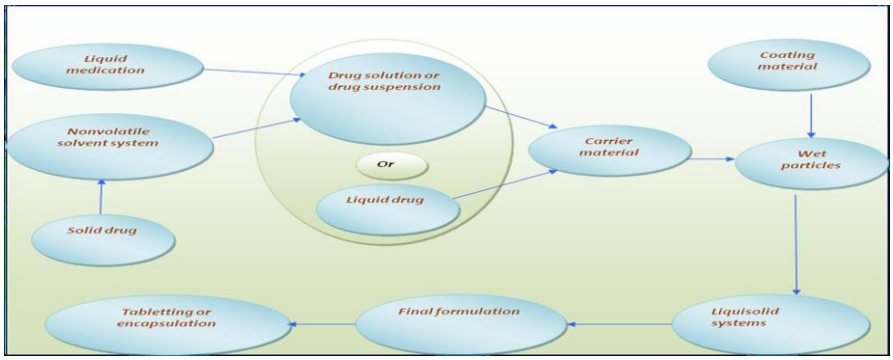

Fig. no. 2: Steps in preparation of Efaverinz Liquisolid compacts

MATERIALS AND METHODS

Efaverinz, Propylene glycol, Poly ethylene glycol-400, Tween-80, Microcrystalline, Cellulose-102, Sodium starch glycolate, Aerosil-200, Magnesium stearate, Talc.

Disintegration time:

The U.S.P. device to test disintegration uses 6 glass tubes with 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 20 C Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles/min. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets.

Drug release

The drug release from the Efaverinz tablets was investigated in a USP-II (paddle) apparatus, 900 ml of Phosphate buffer pH 6.8 with 2% SLS (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and diluted to suitable concentration and then analyzed with UV spectrophotometry at $\lambda max = 248$ nm.

Stability studies:

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing.

1. 250C/60% RH analyzed every month for period of three months.

2. 300C/75% RH analyzed every month for period of three months.

3. 400C/75% RH analyzed every month for period of three months.

Formulation Development

Manufacturing process:

Step 1: take required quantity of PG into a mortar.

Step 2: Add intragranular part of MCC to it and mix well to form unfirom mix / mass.

Step 3: Add intragranular part of Aerosil to step 2 and mix further to form dry flowable powder mass.

Step 4: Sift the material of step 3 through # 40 mesh.

Step 5: Add extragranular MCC, Crospovidone to step 4 and blend well. Add mg stearate and blend well.

Step 6: Compress the blend into tablets using suitable punch.

Table no. 3: Composition of Efaverinz Tablets:

Formulations of Liqui solid compacts of Efavirenz									
S.no	**Ingredients**	**mg / tab**							
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Efavirenz	100	100	100	100	100	100	100	100	100
2	PG	12.5	25	50	0	25	0	25	0	25
3	Polysorbate 80	0	0	0	0	0	0	0	0	0
4	PEG 400	0	0	0	0	0	0	0	25	0
5	PVP K30	15	15	15	0	0	0	15	15	0
	HPC-Lp	0	0	0	0	15	15	0	0	0
6	MCC	83.5	75	66	100	75	91	37.5	75	75
	Crospovidone	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
7	Lactose	0	0	0	0	0	0	37.5	0	0
8	AEROSIL	3	3	3	3	3	3	3	3	3
	Extragranular									
9	MCC	45	41	25	56	41	50	41	41	56
11	Crospovidone	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
12	Mg stearate	1	1	1	1					
Total tablet weight		275	275	275	275	275	275	275	275	275

RESULTS AND DISCUSSIONS

Table no. 4: Pre Formulation Study

S.no	API Characterisation	Results
1	Physical Appearance	a white to slightly pink crystalline powder
2	Melting point	138-148 ºC
3	Bulk density	0.376 gm/ml
4	Tapped Density	0.421 gm/ml
5	Carr's index/Compressibility index	11.9
6	Hausner's Ratio	1.119

The value of compressibility index above 25%, 15-25%, less than10% indicates poor flowability, optimum flowability and high flowability respectively. As Efaverinz value is <10 so it exhibits good flow.

Table no. 5: Solubility Studies

Solvent	Solubility (mg/ml)
Water	0.123
Polyethylene Glycol-400	2.253
Propylene Glycol	20.52
Tween 80	9.653333
Buffer pH (6.8)	0.194

Drug polymer interaction study:

From the spectra of Efaverinz, combination of Efaverinz with excipient, it was observed that all characteristic peaks of Efaverinz were present in the combination spectrum, thus indicating compatibility of the drug and excipient. IR spectra are shown in Figures. The samples were analyzed in the 2500–500 cm^{-1} range, within which the most important peaks for the evaluation

of efavirenz lie.

Table no. 6: Characteristics FTIR spectrum bands of EFV

Frequency (cm^{-1})	Vibrational Assignments
2260	Typical exocyclic triple bond stretching
1757	C= O Stretching
1602	Tertiary Amide
900-650	Aromatic Ring
1350-1120	CF_3
1096-1089	C-Cl Stretching

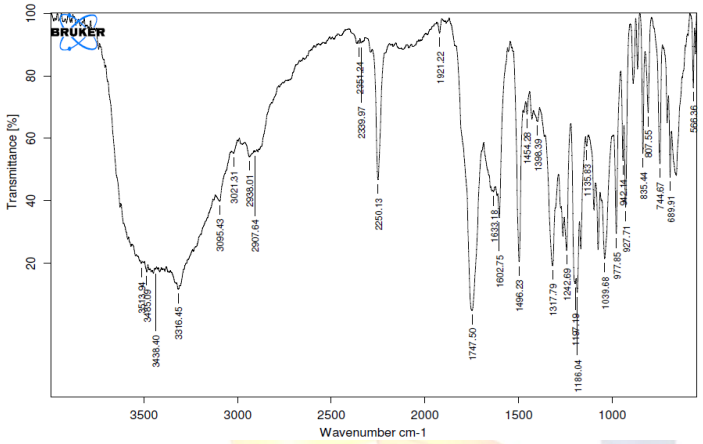

Fig. 5: IR spectra of Efaverinz+HPC

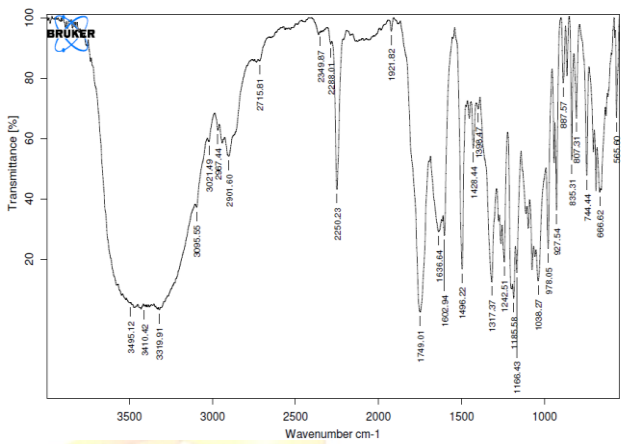

Fig. 6: IR spectra of Efaverinz+MCC

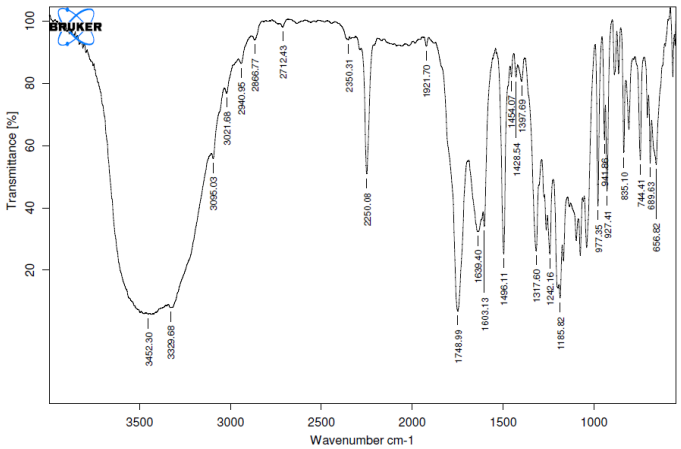

Fig. 7: IR spectra of Drug+AEROSIL

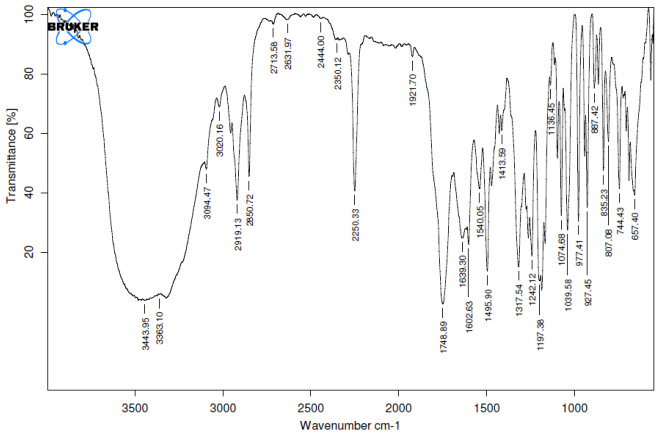

Fig. 8: IR spectra of the Optimized Formulation

Table 6: Standard calibration curve for Efaverinz in 6.8 phosphate buffer of 2% SLS:

Concentration (µg/ml)	Absorbance (nm)
0	0
2	0.116
4	0.219
6	0.314
8	0.415
10	0.513

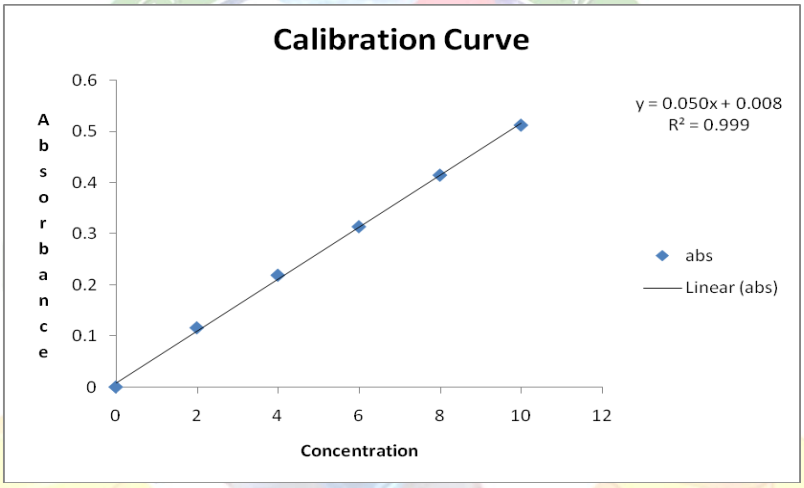

Fig. no. 9: Standard calibration curve for Efaverinz

Table no. 7: Flow properties:

Formulation	Bulk	Tapped	Carr's	Hausner's	Angle
F1	0.318	0.389	18.25	1.223	24.93
F2	0.331	0.399	17.04	1.205	24.25
F3	0.329	0.396	16.91	1.203	25.05
F4	0.345	0.409	15.64	1.185	26.40
F5	0.338	0.378	10.58	1.118	28.67
F6	0.389	0.444	12.38	1.141	27.56
F7	0.362	0.410	11.70	1.132	27.66
F8	0.329	0.396	16.91	1.203	28.67
F9	0.337	0.403	16.31	1.195	25.06

Evaluation studies of tablets:

Table 8: Evaluation studies of formulation

Formulation	Weight	Hardness	Thickness	Friability	Drug Content
F1	275±0.13	3.6	1.85	0.15%	95.69
F2	275±0.53	3.5	1.9	0.12%	94.67
F3	274±0.69	4.1	1.91	0.14%	96.19
F4	274±0.11	3.9	1.95	0.12%	93.67
F5	275±0.16	3.5	1.86	0.13%	98.16
F6	275±0.17	3.3	1.92	0.12%	94.17
F7	276±0.18	3.4	1.91	0.14%	95.18
F8	274±0.10	3.8	1.93	0.16%	97.16
F9	275±0.03	3.5	1.87	0.15%	96.20

The hardness of the all formulations was found to be 3.3 to 4.1 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 1.85 to 1.98. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. ±7.5%. The drug content was found to be 99.02 to 99.8%, indicating uniform distribution of drug in the tablets.

Disintegration time of all formulations

The most important parameter that needs to be optimized in the development of fast disintegrating tablets is the disintegration time of tablets. In the present study disintegration time of all batches were found in the range of 12 to 20 sec fulfilling the official requirements (less than1 min) for disintegrating tablets.

In vitro dissolution studies:

Apparatus: I

Solvent: 6.8 pH phosphate buffer with 2%w/w SLS

Volume: 900 ml

Rpm: 50

Temperature: 37 ± 5˚C

λ_{max}: 248 nm

Table no. 9: Dissolution profile of prepared formulations

	Percentage Cumulative Drug Release								
Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	61	68	74	35	71	49	65	65	55
15	74	79	85	44	83	63	78	76	64
20	81	88	85	58	92	76	87	89	76
30	90	92	85	67	97	82	94	94	90
45	92	94	85	70	98	90	96	97	92

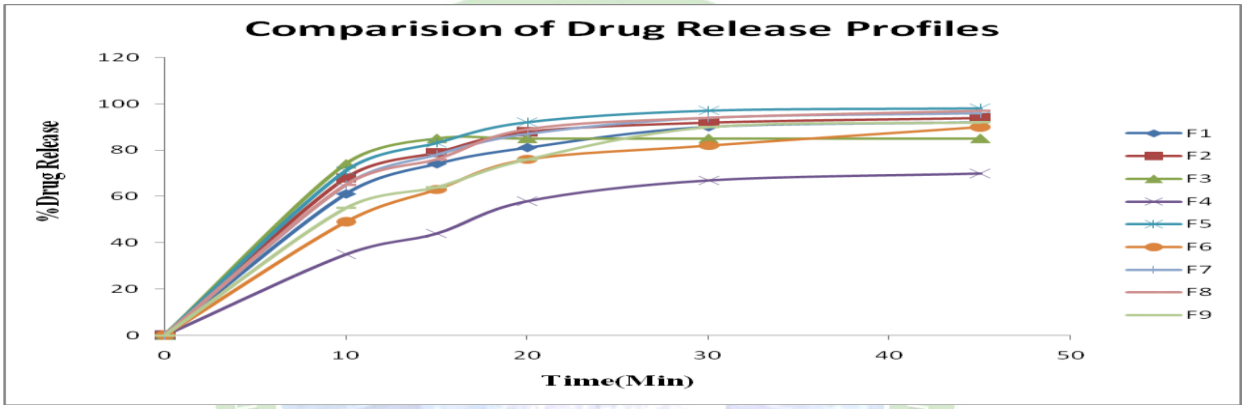

Fig. no. 10: Dissolution profile of prepared formulations

Stability studies:

There were no significant changes in physical and chemical properties of capsule of formulation F-5 after 2 months. Parameters quantified at various time intervals were shown:

Table no. 10: Results of stability studies of optimised formulation F5:

Formulation code	Parameters	Initial	1st Month	2nd Month	Limits as per specifications
F5	25˚C/60%RH	98	97.87	97.65	Not less than 85%
F5	30˚C/75%RH % Release	98	97.89	97.88	Not less than 85%
F5	40˚C/75%RH % Release	98	97.88	97.63	Not less than 85%
F5	25˚C/60%RH Assay value	98.16	98.10	98.12	Not less than 90%
F5	30˚C/75%RH Assay value	98.12	98.11	98.10	Not less than 90%
F5	40˚C/75%RH Assay value	98.16	98.10	98.10	Not less than 90%

Table no. 11: Stability dissolution profile of F5 for 1st and 2nd month

S.No	Time (in minutes)	F8 1st Month	F8 2nd Month
1	**0**	0	0
2	**10**	71.65	70.89
3	**15**	83.26	82.59
4	**20**	91.86	91.79
5	**30**	97.05	96.39
6	**45**	97.69	97.99

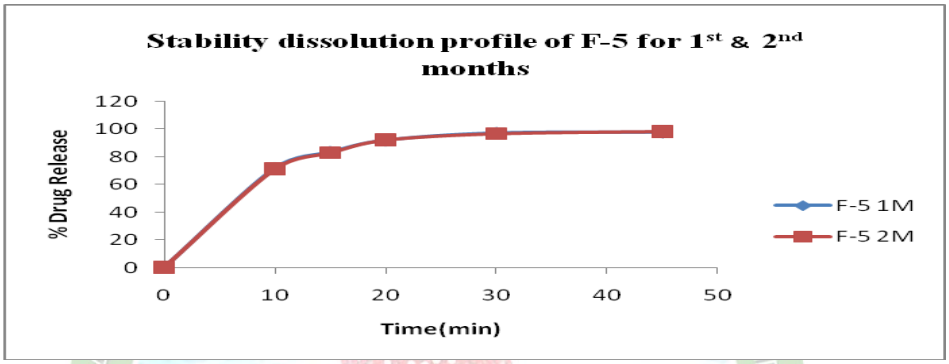

Fig. no 11: Stability Dissolution Profile of F-5 for 1st & 2nd months

CONCLUSION

The aim of this study was to improve the dissolution profile thereby increase solubility. From the results obtained from executed experiments it can be concluded that:

- The preformulation studies like melting point, flow properties, UV analysis of Efaverinz were compiled with IP standards.
- The FTIR spectra revealed that, there was no interaction between polymer and drug. Polymers used were compatible with Efaverinz.
- In vitro drug release of Efaverinz compacts showed increase in dissolution rate of Efaverinz. So PEG 400, PG, Tween 80 could be economic substitute as dissolution enhancing agent.
- Stability studies showed that there were no significant changes in physical and chemical properties of formulation F5 after 2 months
- Propylene glycol in 1:0.25 ratio (F5) was showing best release. F5 was compared with

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