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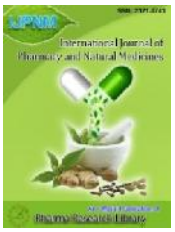

Research Article Open Access

Formulation and Evaluation of Quitiapine Fumerate Liquisolid Compacts

Ch. Srilatha[1], K. Sindhu[1]*, Dr. M. Ravi Kumar[1], Dr. K. Someshwar[2]

[1]*Geetanjali College of Pharmacy, Keesara, Rangareddy, Telangana, India*
[2]*Manager, Formulation R&D, Karthikeya Drugs and Pharmaceuticals Private Limited, Kothapet, Hyderabad.*

A B S T R A C T

The purpose of this study is to develop novel a liquisolid technique to enhance the dissolution rate of poorly water soluble drug Quitiapine fumerate. The main components of a liquisolid system are a non volatile solvent, carrier and coating materials and a disintegrant. Liquisolid system refers to the formulations that are formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents into dry, non adherent, free flowing and compressible powder mixture by blending with suitable carrier and coating materials. Hence the dissolution step, a pre-requisite for drug absorption, is by passed and better bioavailability of poorly soluble drug is achieved. Liquisolid tablets of Quitiapine fumerate are prepared by using PEG as non volatile liquid vehicles and Avicel PH 101, Aerosil as carrier and coating materials respectively. Optimized formulation containing 20% drug in PEG 400, with Avicel 200 as carrier and Aerosil as coating material has shown 98.4% drug release within 20 min .The results are found to be satisifactory.

Keywords: Quitiapine fumerate, Liquisolid compacts, Coating material

A R T I C L E I N F O

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***Corresponding Author**
K. Sindhu
Geetanjali College of Pharmacy,
Keesara, Rangareddy, Telangana, India
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1. Introduction

It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the G.I.T. The poor dissolution of water insoluble drugs is a substantial problem confronting the

pharmaceutical industry. The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid at the absorption site. The dissolution rate is often the rate-determining step in drug absorption.[1] Therefore, the solubility and dissolution behavior of a drug are the key determinants of the oral bioavailability. These two aspects form the basis of the Biopharmaceutical classification system (BCS).

Strategies to Increase the Amount of Dissolved Drug at the Absorption Site: Different approaches have been attempted to increase aqueous solubility of poorly soluble drugs, such as conversion of crystalline molecule to its amorphous state, a particle size reduction via micronization, solubilization in surfactant systems, cosolvency, hydrotropic solubilization, cyclo dextrincomplexation. However, there are some practical limitations of the above-mentioned techniques. Salt formation may increase hygroscopicity leading to stability problems. Solubilization technique lead to liquid formulations those are usually undesirable from patient acceptability and commercialization. The most common method to increase the surface area of the drug is micronization. But, in practice the effect of micronization is often disappointing, especially when the drugs are encapsulated or tableted. Micronised drugs also have the tendency to agglomerate as a result of their hydrophobicity, thus reducing their available surface area. Solid dispersions improve solubility, wettability, dissolution rate of the drug. However, only few solid dispersion products are commercially available. This is due to poor physical characteristics for dosage form formulation. Similarly use of large quantity of organic solvent in preparation of solid dispersions may pose environmental and safety concerns. The surface solid dispersions were introduced to overcome these shortcomings. But still there are limitations of this technique which lie with the use of solvents for preparation of surface solid dispersions. Finding a suitable solvent to dissolve the drug and carrier is difficult. Complete removal of solvent is difficult and residual solvent toxicity should be considered. Inclusion of drug solutions or liquid drugs into soft gelatin capsules or specially sealed hard gelatin capsules are the formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs .Despite their high production cost and technologically demanding, patented and advanced preparations, soft gelatin capsules represent a unique approach for the formulation of liquid oily medications and/or drug solutions of water-insoluble solid drugs. When comparing various oral solid dosage forms, soft gelatin capsules gave the highest and most consistent bioavailability, mainly due to the fact that the drug is already in solution. The availability of drug for absorption from various types of oral formulations usually decreases in the following order: Solution, suspension, powdered filled capsule, compressed tablet, coated tablet. The main disadvantage of soft gelatin capsules is their high production cost. Therefore, a more recent technique, entitled “powdered solution technology”, has been applied to prepare water-insoluble drugs into rapid-release solid dosage forms. Powdered solutions are designed to contain liquid medications in powdered form. The concept of powdered solutions enables one to convert a liquid drug or poorly water-soluble solid drug dissolved in a suitable non-volatile solvent into a dry, non-adherent, free-flowing and readily compressible powder by its simple admixture with selected carrier and coating materials. This method does not involve drying or evaporation. It is well established that better bioavailability of a relatively water-insoluble drug is achieved when the drug is in solution form. That is why soft gelatin capsules of such drugs demonstrate higher bioavailability compared to the conventional oral solid dosage forms. The same principle governs powdered solutions and is solely responsible for their improved dissolution profiles. In this instance, even though the drug is in a tabletedor encapsulated dosage form, it is held in solution thus enhancing its release. Liquid lipophilic drugs (e.g., chlorpheniramine and clofibrate) or solid drugs (e.g., prednisone, prednisolone, hydrocortisone, theophylline, polythiazide and spiranolactone) dissolved in nonvolatile, high-boiling point solvent systems (e.g., polyethylene & polypropylene glycols ,glycerin, N,N-dimethylacetamide, various oils) have been formulated in powdered solutions by admixture with various carriers (e.g., cellulose) and coating materials (e.g., silica). This technique has been reported to produce improved dissolution profiles as compared to the commercially available products.

2. Materials and method

Materials: Quitiapine Fumate, PEG 400, cross povidone, avisol, aerosol.

Methodology

Preformulation Studies: Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Analytical method development:

a) Determination of absorption maxima: A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The χ maxwas found to be 284nm. Hence all further investigations were carried out at the same wavelength.

b) Preparation of standard graph in 0.1 N HCl

100 mg of Quitiapinefumerate was dissolved in methanol 5 ml, volumetric flask make up to 100 ml of 0.1 N hydrochloric acid, from this primary stock 10 ml was transferred to another volumetric flask made up to 100ml with 0.1 N HCl, from this secondary stock was taken separately and made up to 10 ml with 0.1 N hydrochloric acid, to produce 10, 20, 30, 40, 50, 60, 70, 80 µg/ml respectively. The absorbance was measured at 284 nm by using a UV spectophotometer.

Preformulation Studies:

Solubility studies: For the selection of best non volatile solvents solubility studies are used, in this procedure, pure drug was dissolved in five different non volatile solvents. Excess amount of pure drug was adding to the non volatile solvents. From this obtained saturation solution were

shaking on the rotary shaker for 48 hours at 25 ^{0}C under constant vibration. After 48 hours period the saturated solution were filtered through a filter paper, and analyzed by UV spectrophotometer. The liquisolid tablets contain a solution of the drug in suitable solvent, the drug surface available for dissolution is tremendously increased.

Calculation of loading factor (L_f)

Loading factors were calculated for different carriers, using various solvents. By using L_f = W/Q formula (W: Amount of liquid medication and Q: Amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. The results showed that if the viscosity of the solvent is higher, lower amounts of carrier and coating materials are needed to produce flowable powder.

Formulation Development:

Preparation of liquisolid tablets

Preparation of drug solution: For the preparation of liquisolid compacts of Quitiapine fumerate, a non-volatile solvent is chosen for dissolving the drug. From the results of solubility studies and evaluation of flow properties, liquisolid powders containing PEG 400 as the liquid medicament, Avicel pH 101 as carrier and Aerosil pH 200 as the coating material is selected for the preparation of liquisolid compacts. Various ratios of carrier to coating materials are selected. According to solubility of Quitiapine fumerate, desired quantities of drug and PEG 400 were accurately weighed in a beaker and then stirred with constantly, until a homogenous drug solution was obtained. Selected amounts (W) of the resultant liquid medication were incorporated into calculated quantities of carrier contained in a mortar.

Mixing: The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rotation/sec for approximately one minute in order to evenly distribute the liquid medication into the powder. In the second mixing stage, calculated quantities of coating material was added to the system and blended for 2 min. the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5min to allow the drug solution to be absorbed in interior of the powder particles. In the third stage, the powder was scraped off the mortar surfaces by means of aluminium spatula and then blended with a calculated quantity of disintegrant (5%) for another 30sec, in a manner similar to the one used in the first stage, producing the final liquisolid formulation to be compressed. The tablets were prepared by compressing the thoroughly mixed materials using 6 mm round, flat and plain punches on a 8 station tablet machine (Cemach India). The thickness of the tablet was 3.6mm.

Evaluation of Liquisolid Tablets.

Pre Compression Parameters:

Measurement of Micromeritic Properties of Powders

1. Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface.

2. Bulk density

The power sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_0 is noted.

3. Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are proceeded further for an additional tapping 750 times and tapped volume, V_b is noted.

4. Compressibility Index

The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) /TD] x100 ..... (4)

5. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio.

Post Compression Parameters:

a) Thickness: The thicknes of liquisolid tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

b) Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviatefrm the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

c) Friability: The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.

e) Disintegration test: Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

f) Dissolution test of Quitiapine fumerate liquisolid tablets: Drug releaase from Quitiapine fumerate liquisolid tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were 0.1N HCl as the dissolution medium of quantity 900ml. The whole study is being carried out at a temperature of 37^0 C and at a speed of 50rpm. 5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 20 mimutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after

appropriate dilution by UV spectrophotometer. The concentration was calculated using standard calibration curve.

3. Results and Discussion

The present study was aimed to developing liquisolid compacts of Quitiapine fumerate to improve its solubility and dissolution rate.

Analytical Method: Graphs of Quitiapine fumerate was taken in Simulated Gastric fluid (pH 1.2) .

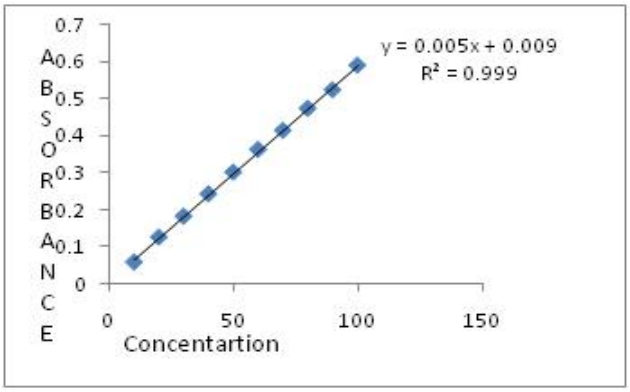

Figure 1: Standard graph of Quitiapinefumeratein0.1N HCl

The linear equation was: Absorbance = 0.0058 x concentration (µg/ml) +0.0064. Different standard concentration and their absorbance values were shown in the table. At all the concentration levels the standard deviation (SD) was low. Goodness of fit of regression equation was supported by high regression value (0.9994). Hence the developed method can be used for routine analysis of model in pharmaceutical formulations and for dissolution studies.

Solubility studies: The solubility of drug was found to be more in PEG 400. So it was preferred as non volatile solvent. Formulation trails were also done with other solvents, because according to published evidence there are chances that the drug in dispersed state can also be formulated as liquisolid tablet to increase release rate.

Characterization of Pre Compression Parameters of All Tablets: Powder flow is a complicated matter and is influenced by so many interrelated factors; the factors' list is long and includes physical, mechanical as well as environmental factors Therefore, in our study, because of the subjective nature of the individual types of measurements as indicators of powder flow, three flow measurement types were employed; the angle of repose, Carr's index (compressibility index), and Hausner's ratio. As the angle of repose (Θ) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non cohesive. F1, F5 and F9 (θ=33.9±0.4, θ=33.5±0.5, θ=33.5±0.5) were chosen as liquisolid systems with acceptable flow ability according to the angle of repose measurements, while those having higher angles of repose were considered as non-acceptable.

Powders showing Carr's index (%) up to 21 are considered of acceptable flow properties. In addition to Carr's index, Hausner found that the ratio $D_{Bmax/DBmin}$ was related to the inter particle friction, so, he showed that powders with low inter particle friction, had ratios of approximately 1.25 indicating good flow. Therefore F1, F5, F6, F9 were selected as acceptably flowing as they had average Ci (%) of 14.2±0.3, 12.5±0.6, 13.3±0.9; 10.4±0.1 respectively and average Hausner's ratios of 1.16±0.01;1.11±0.02; 1.15±0.01; 1.17±0.02; in the same order. Finally, formulae F3, F5, F7, F12, were proven to be acceptably flowing according to either the angle of repose, Carr's index and Hausner's ratio were compressed into tablets and subjected for further evaluation while the rest of formulae were nominated as having unacceptable flow ability and therefore excluded from further investigation. At this microenvironment, it may be possible that the infinite amounts of PEG 400 diffusing with the drug molecules out of a single liquisolid particle and excessive amount of Avicel PH 200 responsible for its disintegration property. F1 and F5 formulations also showed the higher dissolution profiles (96.4%, 98.4%) when compared to the rest of the three formulations in 10% (F2=94.6%, F3=93.4, F4=92.3) and 20% (F6=95.3, F7=93.3, F8=90.14). This may be due to the higher amount of Aerosil ® PH 200 which aid in adsorbing excessive amount of liquid in the physical mixture.

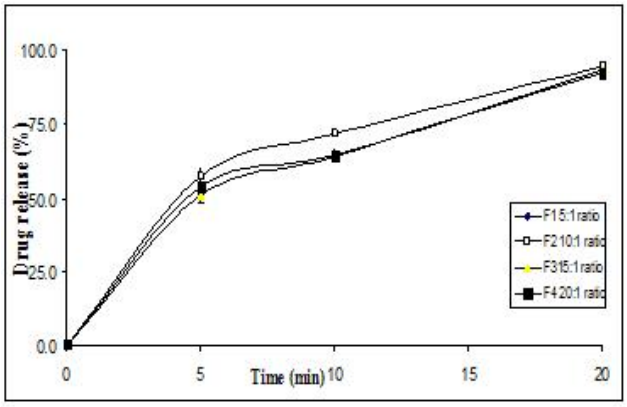

Figure 2: Dissolution profiles of PEG 400 10% drug solution of Quitiapine fumerate liquisolid tablets. Data represents mean ± S. D (n=3).

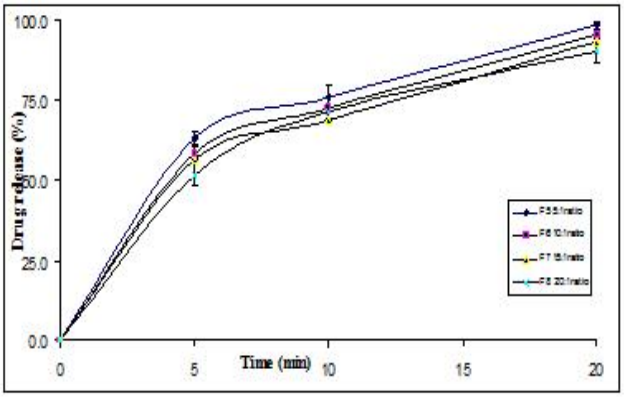

Figure 3: Dissolution profiles of PEG 400 20% drug solution of Quitiapine fumerate liquisolid tablets data represents mean ± S. D (n=3).

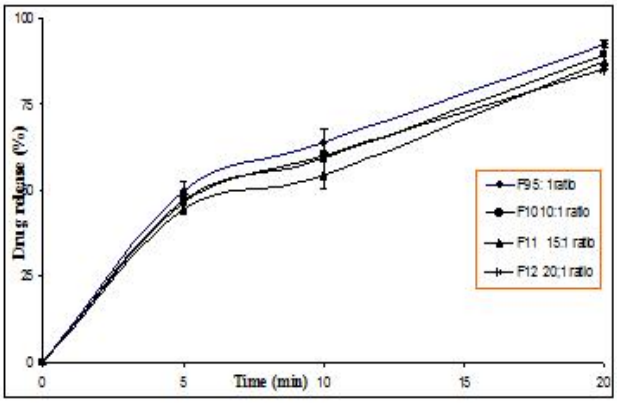

Figure 4: Dissolution profiles of PEG 400 30% drug solution of Quitiapine fumerate liquisolid tablets data represents mean ± S. D (n=3).

Liquisolid formulations (F9,F10, F11, F12) containing 30% drug solution in the Figure 7.6 showed lowest drug release profiles (92.3%, 89.4%, 87.3%,85.1%) when compared to 10% drug solution and 20% drug solution , Because of low amount of PEG 400, in these formulations drug is dispersed in the solvent, formed as drug suspension further showing no change in drug state. But, these formulations are showing excellent flow properties may be due to low amount of PEG 400. These evaluation parameter of these four formulations observed in acceptable range.

4. Conclusion

In the present study Quitiapine fumerate liquisolid compacts were developed to improve the solubility and dissolution rate. Of the all liquisolid formulations prepared F5 was found to be optimized formulation as it showing desired release along with acceptable physical properties. Our main aim was to improve the dissolution behaviour by improving the physical properties.F5 was showing 98.4 % release hence it was considered as optimized formula. From the above discussions it can be concluded that F5 formulation having 20% drug concentration in PEG, with R value 5 and Lf value 0.312 was showing 98.4% release. Hence it can be appealed for further research.

5. Acknowledgement

The authors sincerely acknowledge the KP Labs (A Diviison of Karthikeya Drugs & Pharmaceuticals Private Limited), Kotahpet, Hyderabad, for providing Drugs and support to carry out this research work.

Table 1: Composition of liquisolid tablets

Formulation	Quitiapine fumerate conc. PEG 400	R	L_f	Avicel PH 200 (mg)	Aerosil PH 200 (mg)	Total tablet weight (mg)
F1	10%	5	0.312	200	80.0	635.0
F2		10	0.312	200	40.0	592.5
F3		15	0.312	200	26.5	579.0
F4		20	0.312	200	20.0	572.5
F5	20%	5	0.312	200	40.0	317.5
F6		10	0.312	200	20.0	295.5
F7		15	0.312	200	13.2	288.2
F8		20	0.312	200	10.0	285.0
F9	30%	5	0.208	200	40.0	294.1
F10		10	0.208	200	20.0	274.1
F11		15	0.208	200	13.2	267.3
F12		20	0.208	200	10.0	264.1

Note: All formulations contain 5% crospovidone as a super disintegrant.
L_f = Load factor; R= carrier and coating material ratio; PEG 400 =Poly ethylene glycol 400

Table 2: Observations for graph of Quitiapine fumerate in 0.1N HCl

S.No	Concentration (µg/ml)	Absorbance
1	10	0.06
2	20	0.127
3	30	0.183
4	40	0.243
5	50	0.301
6	60	0.362
7	70	0.413
8	80	0.472
9	90	0.522
10	100	0.588

Table 3: Solubility studies of Quitiapine fumerate in non volatile solvents

S.No	Solvent	Solubility (mg/ml)
1.	PEG 400	125
2.	PEG 200	110
3.	Glycerin	90
4.	Propylene Glycol	40
5.	Tween 80	25

Micromeritic properties of Powder blends of different batches

Table 4: Evaluation parameters of tablets containing PEG 400 10% drug solution by using Avicel PH 200 as carrier

Evaluation Parameters	F1	F2	F3	F4
Angle of repose	35.5±0.6	37.9±0.7	38.2±0.4	39.5±0.5
Bulk density(gm/cc^3)	308.3±1.4	303.7±1.6	304.1±1.2	304.2±1.3
Tapped density (gm/cc^3)	359.7±1.6	379.6±1.2	396.0±1.8	391.6±1.6
Carr's index (%)	14.2±0.3	19.9±0.3	23.2±0.8	22.3±1.2
Hausner's ratio	1.16±0.01	1.24±0.02	1.31±0.01	1.28±0.01

Data represents mean ± S. D (n=3)

Table 5: Evaluation parameters of tablets containing PEG 400 20% drug solution by using Avicel PH 200 as carrier

Evaluation parameters	F5	F6	F7	F8
Angle of repose	25±0.2	34.7±0.3	36.2±0.4	36.4±0.4
Bulk density(gm/cc^3)	206.5±1.6	206.6±1.9	209.1±1.6	206.8±1.2
Tapped density (gm/cc^3)	235.7±0.2	238.4±0.9	252.6±0.5	250.0±0.8
Carr's index (%)	12.5±0.6	13.3±0.9	17.2±0.4	17.28±0.3
Hausner's ratio	1.14±0.02	1.15±0.01	1.2±0.01	1.2±0.01

Data represents mean ± S. D (n=3)

Table 6: Evaluation parameters of tablets containing PEG 400 30% drug solution by using Avicel PH 200 as carrier

Evaluation Parameters	F9	F10	F11	F12
Angle of repose	33.5±0.1	34.9±0.2	34.8±0.4	35.4±0.3
Bulk density(gm/cc^3)	206.0±1.1	199.3±1.3	194.6±1.9	192.4±1.8
Tapped density(gm/cc^3)	230.0±0.6	255.9±0.9	241.8±0.9	279.1±0.8
Carr's index (%)	10.4±0.1	17.5±0.*8*	15.4±0.9	16.9±0.6
Hausner's ratio	1.11±0.02	1.28±0.02	1.23±0.02	1.45±0.01

Data represents mean ± S. D (n=3)

Table7: Evaluation parameters of tablets containing PEG 400 10% drug solution by using Avicel PH 200 as carrier

Evaluation parameters	F1	F2	F3	F4
Hardness (kg/cm^2)	4.5±0.3	4.4±0.2	4.4±0.4	4.5±0.3
Disintegration time (sec)	190±4	220±5	160±5	170±4
Thickness (mm)	4.6±0.02	4.5±0.02	4.5±0.02	4.4±0.01
Weight variation(mg)	636.5±1.3	595.3±1.7	580.0 ±1.3	575.8±1.5
Friability (%)	0.76	0.45	0.43	0.45
Content of uniformity (%)	98±0.2	98.8±0.8	97.5±0.6	99.2±0.5
% Cumulative drug release (20 min)	96.4±0.2	94.6±1.3	93.4±1.2	92.4±2.3

. Data represents mean ± S. D (n=3).

Table 8: Evaluation parameters of tablets containing PEG 400 20% drug solution by using Avicel PH 200 as carrier

Evaluation parameters	F5	F6	F7	F8
Hardness (kg/cm^2)	5.9±0.4	5.8±0.2	5.8±0.2	5.7±0.3
Disintegration time (sec)	115±5	100±4	90±5	90±4
Thickness (mm)	3.0±0.01	3.1±0.01	3.0±0.01	3.1±0.02
Weight variation(mg)	318.2±1.7	300.0±1.6	290.5±1.5	288.1±1.9
Content of uniformity (%)	99.6±0.6	96.8±0.3	99.6±0.4	96.6±1.2
% Cumulative drug release (20 min)	98.4±1.4	95.4±2.1	93.3±0.9	90.1±3.3

Data represents mean ± S. D (n=3).

Table 9: Evaluation parameters of tablets containing PEG 400 30% drug solution by using Avicel PH 200 as carrier

Evaluation parameters	F9	F10	F11	F12
Hardness (kg/cm^2)	6.1±0.4	5.5±0.3	5.9±0.2	5.8±0.2
Disintegration time (sec)	120±2	130±5	150±5	140±5
Thickness (mm)	2.9±0.02	3.0±0.01	2.9±0.02	2.8±0.02
Weight variation(mg)	295.1±3.2	280.1±3.0	271.5±2.8	266.7±3.3
Friability (%)	0.34	0.25	0.34	0.26
Content of uniformity (%)	96.8±0.9	97.2±0.5	99.2±0.5	97.6±0.2
% Cumulative drug release (20 min)	92.3±1.3	89.4±1.9	87.4±2.1	85.1±1.7

Data represents mean ± S. D (n=3)

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