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Development and Evaluation of Quercetin Dispersible Tablets

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Research Article

Development and Evaluation of Quercetin Dispersible Tablets

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Abstract

Quercetin is an anti-oxidant agent, commonly used as an anti-inflammatory, anti-rheumatic, anti-diabetic, anti-ulcer, and is also used for the treatment of several cancers such as bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, prostate and others. In the present study, dispersible tablets of Quercetin, using three different disintegrants such as Crospovidone, Amberlite IR P 88 with different ratios, and complexatation done with Soluplus by Hot Melt Extrusion (HME) Method, was prepared and the solubility of Quercetin was increased. All formulations were studied in terms of pre-compressional parametres (flow properties) such as bulk density, tapped density, angle of repose, Carr's index and post compressional studies such as weight variation test, disintegration time, dispersion time, friability test, drug release and study. Optimized formulation F6 was evaluated for pharmacokinetics parametres, anticancer activities and stability studies as per ICH guidelines.

Key words: Anticancer Activity Study, Dispersible Tablets, Evaluation Parametres, Pharmacokinetics Parametres, Quercetin, Stability Study

1. Introduction

A system in which the drug product is in a form of tablet, which disintegrates and dissolves within a minute or in a few seconds after administration is known as dispersible tablet system. Therefore, in this type of system, the drug bioavailability might be greater than a conventional oral dosage form. Dispersible tablet system consists of a disintegrating and super-disintegrating asset in which water enters the tablet matrix quickly, which in turn results in a generation of porous structure that results in a fast disintegration. Hence, for the development of the dispersible tablet, it comprises the exploitation of tablet matrix that is made up of a porous structure by the incorporation of suitable disintegrating agents, or it may be done by adding hydrophilic excipients in the formulation. The development of the tablet can also be obtained by using a direct compression method.[1-3]

In industries, direct compression method is generally used for developing dispersible tablets as it is simple and cost–effective due to the usage of conventional equipment and commonly used excipients, as these are the limited processing steps that are beneficial to this technique. Solubilization depends on single or multiple actions of disintegrant, hydrophilic excipients and effervescent agents in the directly compressed tablets. The name 'Quercetin' came from the Latin word quercetum, which means oak – forest quercus oak. Bioflavonoids was firstly discovered by Albert Szent Gyorgyi in 1930; he also won the Nobel Prize for the same. Over the past 30 years researchers have been extensively studying about Quercetin (3,3',4'5,7-pentahydroxy flavone), which is a natural unique bioflavonoid.[5] The synonyms of Quercetin are Quercetin, sophretin, meletin.

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It is formed as the glycoside Quercitrin in the bark of quercus tinctoria (American Oak). Several years ago, it was found that Quercetin causes DNA mutation in bacteria, which was a possible sign that it may cause cancer. It was also discovered that in the Quercetin plant, leaves, barks, rinds, seeds and flowers contain a pigment called polyphenolics, which is found associated with Vitamin C that imparts synergistic effects. Flavoinds and Vitamin C both act as antioxidants; therefore, both prevent the Quercetin plant from oxidizing. Because of this, Quercetin became a subject of scientific reports over the last three decades, and it also showed the greatest activity among several flavonoids that have been proved in several experimental models. Flavonoids and Vitamin C are also important for human health.[7] It has been reported as a complete package, i.e., it possesses biological, pharmacological and medical applications, and is also reported as one of the most potent antioxidants. The prime objective of this study is to increase solubility and bioavailability of Quercetin by complexatation with a polymer and using different disintegrates by the direct compression method.

2. Materials and Methods

Quercetin was procured from Ozone International, Mumbai, India. Soluplus was obtained from BASF India Ltd, Mumbai. Amberlite IRP88 was obtained from Cipla Pvt Ltd, Mumbai. Crospovidone was obtained from Ozone International, Mumbai. Sodium starch glycolate was obtained from S D Fine Chem Ltd, Mumbai. Magnesium stearate was obtained from Thomas Baker, Mumbai. Microcrystalline cellulose was obtained from Loba Chemie Pvt Ltd. Sodium saccharin was obtained from Central Drug House Ltd, Delhi. All other chemicals used were of laboratory grade.

2.1 Preparation of Drug Complex with Soluplus Polymer by Hot Melt Extrusion Method:

Solid solutions of Quercetin using Soluplus were prepared by hot melt extrusion in a Thermo Fisher Polylab twin-screw extruder. The Drug: polymer ratio was maintained at 1:1. Extrusion parametres adjusted were as follows:

- RPM : 80°C
- Bar Pressure : 40°C
- Temperature : 60°C - 150°C

Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7	Zone 8	Die
60°C	100 °C	120°C	140°C	150°C	150°C	150°C	150°C

2.2 Formulation of dispersible tablets:

The dispersible tablets (average weight 750 mg) of Quercetin were prepared by direct compression technique using three different disintegrants – Crospovidone, Sodium starchglycolate, and Amberlite IR P88. The composition of dispersible tablets is given in Table 5. Microcrystalline cellulose was used as diluents.

- **Procedure:**
  Separately, all the formulation ingredients were passed through sieve no. 30 mesh. To obtain a uniform mixture, the drug and diluent were mixed gradually in a small portion. After a uniform mixture was obtained, a flavouring agent and a lubricant were added at the end and it was again mixed thoroughly. This blend was then compressed in a 750 mg dispersible tablet

Table 1: Composition of Quercetin dispersible tablet using three different disintegrants

Sr. No	Ingredients	F1 mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 mg	Category
1	Quercetin and Soluplus complex	400	400	400	400	400	400	Antioxidant
2	Crospovidone	100	200	-	-	-	-	Disintegrant
3	Sodium starchglycolate	-	-	100	200	-	-	Disintegrant
4	Amberlite IRP88	-	-	-	-	100	200	Disintegrant
5	Sodium saccharin	15	15	15	15	15	15	Sweetening agent
6	Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5	Lubricant
7	Talc	7.5	7.5	7.5	7.5	7.5	7.5	Guidant
8	Microcrystalline cellulose	220	120	220	120	220	120	Diluent
	Total	**750**	**750**	**750**	**750**	**750**	**750**	

by using 10 mm flat punch rotary punching machine.

3. Evaluation of Quercetin dispersible tablets

3.1 Other preformulation studies

Information gained from the preformulation studies of the API is shown in Table 8. From the obtained results, it is determined that the characteristic flow properties of the API is poor. So, it necessitates the need of altering its flow properties in a certain direction to gain uniform weight.[9,10]

3.2 Apparent solubility study

To overcome the low solubility of Quercetin, apparent solubility, a study of Quercetin was carried out using complexation with soluplus polymer.

It was determined by adding an excess of Quercetin and Quercetin-Soluplus complex to 5ml of water or in octanol in sealed containers made up of glass at room temperature (25-30ºC). This complex was agitated for 24 hours and then centrifuged for 20 minutes at 1000 rpm to remove any excess Quercetin. After centrifugation, the supernatant was collected by filtering the mixture with a membrane filter (0.4 µm), and then to the collected supernatant (1 mL), 9 mL distilled water was added for dilution. After dilution these samples were measured at 322 nm UV spectrophotometrically.[11]

3.3 Post-compressional studies:

Post – compressional studies were conducted on dispersible tablets, which include parametres such as weight variation, hardness, friability, disintegration time, wetting time and content uniformity.[12]

3.4 In vitro drug release studies

Drug dissolution studies were carried out by using USP apparatus 2 (paddle type) at 37 °C ± 0.50, in which phosphate buffer pH 6.8 (900 mL) was used as a dissolution media by keeping paddle rotation speed at 50 rpm, then the absorbance was measured at 265 nm spectrometrically.

3.5 Drug content:

For determining the drug content, 10 tablets were weighed precisely and crushed. The amount equivalent to 200 mg of Quercetin was balanced accurately and mixed in 6.8 pH phosphate buffer. This mixture was then filtered through Whatman filter paper. The filtered solution was then analyzed for drug content by UV-spectrophotometre at 265 nm. Phosphate buffer pH 6.8 was used as a blank.[3]

3.6 In Vivo studies

3.6.1 In Vivo pharmacokinetic studies

Pharmacokinetic study was conducted on Albino rats (weighing around 170 to 200 gm). The animals were divided into two groups (where n=6). They

Table 2: Result of preformulation study of Quercetin

Formulation Code	Angle of Repose (0^0)*	Bulk Density (gm/cm^3)*	Tapped density (gm/cm^3)*	Hausner's Ratio*	Carr's Index (%)*
F_1	18.43±0.21	0.405±0.03	0.440±0.011	1.08±0.028	0.7±1.62
F_2	13.76±0.35	0.414±0.05	0.418±0.024	1.03±0.023	0.4±1.32
F_3	15.78±0.45	0.418±0.08	0.424±0.041	1.08±0.024	0.6±1.54
F_4	16.69±0.28	0.420±0.016	0.448±0.029	1.06±0.026	2.8±1.42
F_5	19.24±0.34	0.455±0.04	0.460±0.03	1.11±0.021	0.5±1.21
F_6	25.34±0.51	0.430±0.09	0.435±0.05	1.01±0.023	0.5±1.86

* Values in ± Standard Deviation where n=3

Table 3: Result of postcompressiotional study of Quercetin dispersible tablet

Formulation	Hardness Kg/cm	Friability (%)	Weight Variation (%)	Wetting Time in Sec.	Disintegration Time in sec.	Drug content
F1	3.51±0.21	0.61	747.90 ±0.28	25.22 ± 1.41	27.29 ±0.25	98.73
F2	3.48±0.35	0.52	744.47 ±0.30	24.90 ± 0.21	26.25 ±0.41	100.97
F3	3.74±0.42	0.61	751.20 ±0.06	24.88 ±0.47	25.00 ±0.65	103.50
F4	3.23±0.62	0.53	749.59 ±0.25	23.28 ±0.25	24.05 ±0.47	101.70
F5	3.56±0.12	0.52	747.89 ± 0.45	24.25 ±0.51	26.00 ±0.51	100..69
F6	3.73±0.41	0.43	749.90 ± 0.09	22.58 ±0.24	23.05 ±0.24	103.71

were given Quercetin dispersion solution of a tablet orally. Blood samples was collected from the tail vein of the rats at 5-minute, 10-minute, 15-minute, 30-minute, 45-minute and 60-minute intervals after the administration of the drug. The collected blood samples were centrifuged for 10 minutes at 3000 rpm. After the centrifugation, the clear solution (supernantant) was collected in a tightly sealed plastic tube containing heparin (anti-coagulant agent). This was stored in – 20 °C till analysis. The pharmacokinetic parametres such as the area under the curve (AUC), peak plasma concentration (C_{max}) and the time to attain peak concentration (t_{max}) were determined by plotting the graph between plasma concentration vs time. To determine the elimination rate of the drug was constant (K_{el}), the semi logarithmic plot of plasma concentration vs time was plotted, whereas the elimination half-life ($t_{1/2}$) was determined by using the formula: $t_{1/2} = 0.693/K_{el}$. For determining AUC statistically, one–way ANOVA at 0.05 levels was applied in a graph pad prism version 5.01 software.

3.6.2 *In Vivo* pharmacodynamic studies

This study was carried out to check the anticancer activity on human lung carcinoma (Cell line- A549). Experiments were performed on cell line-A549 human lung carcinoma at the concentration of 10 µgm, 20 µgm, and 30 µgm. All the experiments were supported in agreement with the procedures approved by the Institutional Animal Ethics Committee (IAEC).

MTT Test

Materials and equipment

- 5 mg MTT (3-(4, 5 dimethyl thizol-2-yl)-2, 5-diphenyl tetrazolium bromide) solution in PBS. Sterilized by filtration. Stored in dark at 4 ^{0}C. Stable for a month.
- 96-Well plates
- Multichannel pipettes
- Microplate reader equipped with a 490 nm filter.

Experimental procedure

- After the xenobiotic cell treatment, the monolayers of the cells were washed gently with luke warm phosphate buffer saline pH 7.4 using a multichannel pipette.
- MTT solution contained in culture media (100 µl) was added to each well in a 10:1 ratio. It is recommended to have some wells in the plate without cells but incubated with MTT solution in order to have blanks of the reading.
- Depending on the cell weight and its activity, cells are kept for 1–3 L in volume in a cell incubator.
- Incubation medium is removed carefully.
- Dimethyl sulphoxide (100 uL) was added onto the plate and then the plate was shaken gently to resuspend the formazan which was formed in MTT assay. Then we wait until a homogenized colour is formed.

Reading of results and calculation

- After resuspending the formazan the absorbance was read at 490 nm of all the wells and blanks.
- The mean absorbance of each wells was calculated by subtracting the blank reading. Then, the results were normalized bearing in mind that the control wells would be 100%, i.e., maximum absorbance obtained articulating the results as percentage of controls.

Using the appropriate method of calculation, normally log it transformation, IC 50 and IC10 can be estimated.[15]

3.7 Stability studies

Procedure:

Stability studies of API as well as the drug product is necessary and it's a major criteria in determining the rationale design and evaluation of dosage form and their stability for accepting the drug product. There are three different types of stability studies such as i) real–time stability studies; ii) intermediate type; iii) accelerated stability studies. As real–time stability studies is inconvenient to carry out as it takes more time to get completed, accelerated stability studies came into picture. Therefore, in the present study, the drug product was exposed to normal conditions of temperature and humidity, and for accelerated studies the drug product was stored under extreme conditions as per the ICH guidelines.

One month accelerated stability study was conducted at 40 ± 2 °C and RH 75 % ± 5 %. After the period of one month the tablets were withdrawn and analyzed for physical characterization, *In Vitro* release study and drug content.[16]

4. Results and Discussion

4.1 Compatibility study

IR spectroscopy of Quercetin (FTIR)

This study was conducted to evaluate the compatibility of API with polymers and other excepients of formulation F4 and F6. The IR spectra of API was found to be the same as that of the standard spectra. The samples were put on KBR plates. The FTIR spectra were recorded at 1cm^{-1} resolution with the range of 400 to 4000 cm.[117] Characteristic peaks of the pure drug as aromatic C–H stretching (3382.64 cm^{-1}, C=O (Keto) Stretching (1667.31 cm^{-1})), OH (hydroxyl) stretching (3382.64 cm^{-1}), OH (hydroxyl) bending (1457.72 cm^{-1}), =C-H bending (1006.16 cm^{-1}), C=C stretching (1515.98 cm^{-1}), and C-O-C stretching (933.33 cm^{-1}). So, it shows the presence of the drug in the Soluplus and other excipients. Figure 1 shows the IR spectra of pure Quercetin, physical mixture of drug and polymers F4 formulation and F6 formulation, and confirms the compatibility of drug with the polymer. The characteristic peaks of the pure drug were compared with the peaks obtained from the combinations that are depicted in Figure 1.

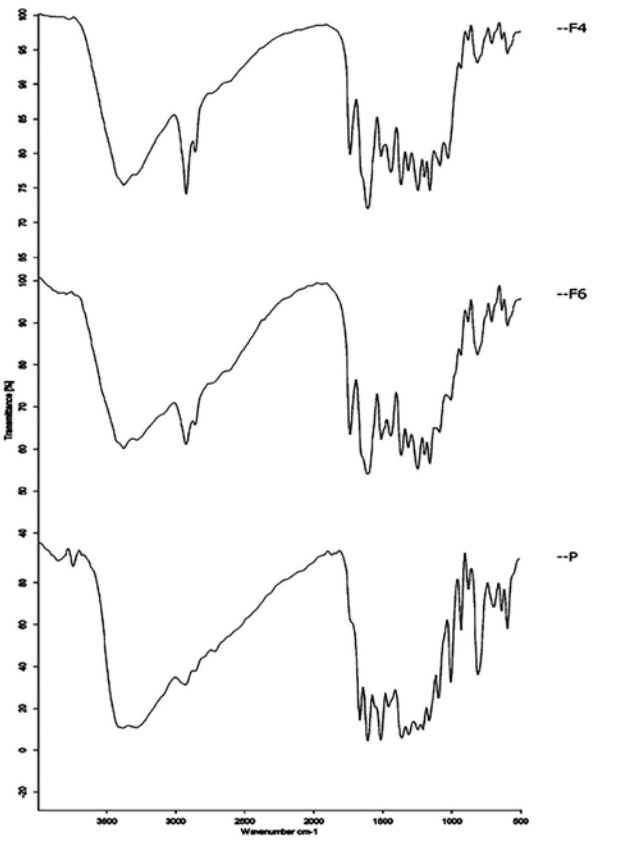

Figure 1: IR spectra of, physical mixture of drug and polymers, formulation F4, formulation F6 and pure drug Quercetin.

4.2 Differential scanning calorimetric

Differential scanning calorimetry is a fast and reliable method to detect drug excipient compatibility to provide maximum information on regarding the possible interactions. In DSC an interaction is concluded by the elimination of endothermic peaks, appearance of new peaks and changes in various parametres of thermogram (like peak shape, its onset, peak temperature/melting point and relative peak area or enthalpy).

Analysis (DSC)

The generated thermograms of DSC showed endothermic peaks of pure (P) Quercetin 314.33 °C, Formulation F6 235.01 °C and 225.05 °C for F4 were observed as shown in Figure 2.

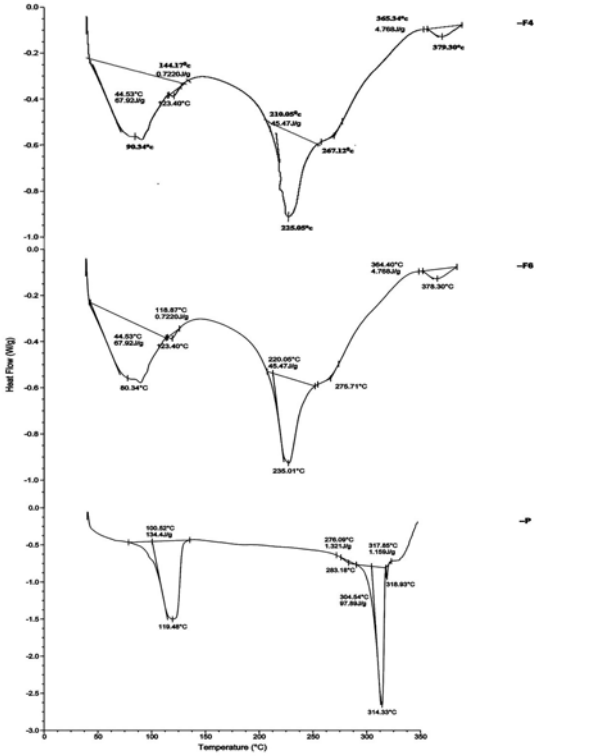

Figure 2: Differential scanning calorimetric graphs of pure (P) Quercetin drug, formulation F6 and formulation F4.

4.3 X-Ray diffraction analysis (XRD)

The physical status of Quercetin soluplus complex (F4 and F6) was compared with that of pure Quercetin (P) by XRD analysis. In Figure 3, Quercetin exhibit a lot of distinct peaks that are traits of a crystalline structure. The Quercetin soluplus complex (F4 and F6) also present a number of distinct peaks. It indicated that the drug was not completely amorphous in nature. The graph shown in Figure 3.17.

4.4 Precompressional studies

Table 2 Result of preformulation study of Quercetin.

4.5 Post compressional Studies

Disintegration time was found between 23.05, 24.05, 25.00, 26.25 and 27.29 (seconds) in six formulations F6, F4, F3, F5, and F1, respectively. By the disintegrating time , it is shown that F6 formulation disintegrate faster compared to the other formulations. Hardness was obtained as 3.25 kg/cm 2, 3.48 kg/cm 2, 3.51 kg/cm 2, 3.56 kg/cm 2, 3.73 kg/cm 2, and 3.74 kg/cm 2 in formulations F4, F2, F1, F5, F6 and F3, respectively.

Table 4: Solubility study (H_2O) at 25°C

Sample	Aqueous Solubility (µg/ml)
Quercetin	3.44
Quercetin complex	30.81

4.6 Solubility studies

The log P value of Quercetin is log P; 1.82 ± 0.32, which indicates the enormous hydrophobicity of Quercetin, but this API is also slightly soluble in aqueous media. Due to the poor solubility nature of Quercetin, it prevents the absorption/permeation across intestinal epithelial cells of GIT, which in turn results in low bioavailability of the drug at the targeted site. Only 3.44 µg/ml of Quercetin is soluble in aqueous media. Therefore, to improve its solubility in aqueous media, it is prepared in a complex form with Soluplus using HME, as mentioned in Table 7. By this, the solubility of Quercetin was increased by 10 folds i.e., 30.81 µg/ ml. HME increased the solubility of the drug by action on wetting time, disintegration time and dispersion time. The Soluplus complexatation increased the solubility behaviour of the herbal actives due to the amphiphilic and amorphous nature of the product. The complex showed enhanced solubility and may improve absorption across the biological barriers for improving oral bioavailability of the active component.

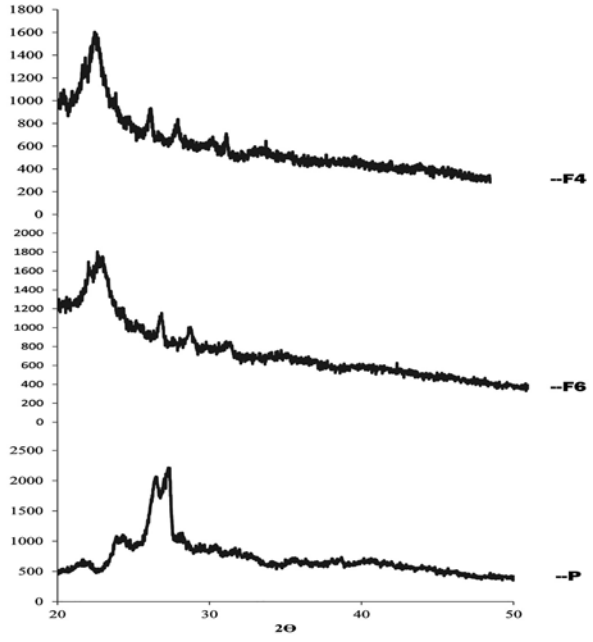

Figure 3: X-Ray powder diffraction studies for Quercetin (P), F6, F4.

Table 5: Drug released profile of formulation of Quercetin dispersible tablet.

Formulation	% Release after 5 min	% Release after 10 min	% Release after 15 min	% Release after 20 min	% Release after 30 min	% Release after 40 min	% Release after 50 min	% Release after 60 min
F1	20.21	25.52	28.05	35.24	38.78	41.24	43.84	49.28
F2	22.58	26.48	30.85	37.58	40.24	44.84	47.18	51.86
F3	10.25	13.27	15.84	22.58	27.56	32.48	37.84	40.57
F4	14.25	18.48	24.45	26.45	30.47	32.85	40.45	41.25
F5	34.24	39.54	42.94	56.35	65.78	70.89	85.28	95.25
F6	**38.09**	**44.08**	**53.84**	**66.66**	**72.72**	**75.76**	**88.70**	**98.25**

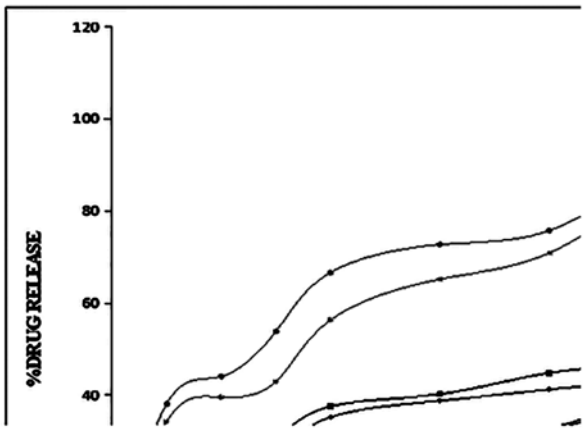

Figure 4: % Drug release V/s time for the Quercetin formulation F1 to F6 In vitro release profile

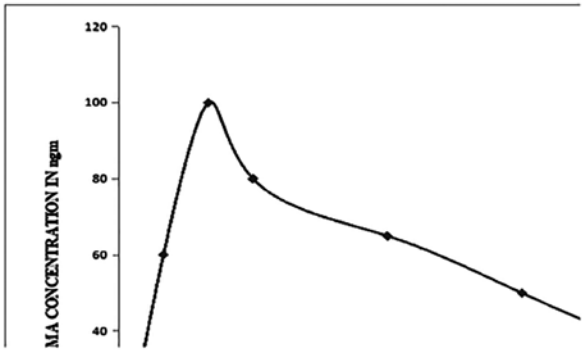

Figure 5: Plasma concentration V/s time profile

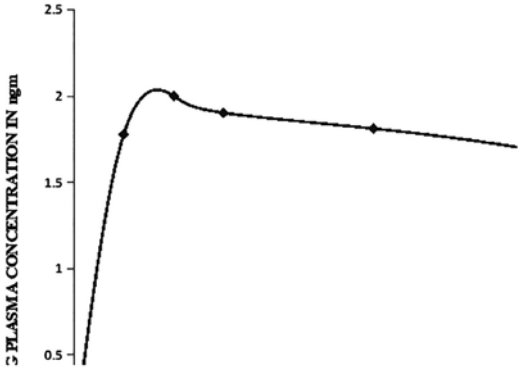

Figure 6: Log plasma concentration V/S time profile

Table 6: Plasma concentration V/S time profile.

Sr. No	Time in minutes	Plasma concentration of formulation F6 in ngm
1	5	60
2	10	100
3	15	80
4	30	65
5	45	50
6	60	35

Table 7: Log plasma concentration V/S time profile.

Sr. No	Time in minutes	Log plasma concentration of formulation F6 in ngm
1	5	1.778
2	10	2.0
3	15	1.9030
4	30	1.812
5	45	1.6989
6	60	1.544

4.7 *In vitro* drug release studies

In vitro release study was carried out for Quercetin dispersible tablet in phosphate buffer pH 6.8 for one hour using dissolution apparatus type USP XXIII. In the present investigation, Quercetin dispersible tablets were prepared in six formulations varying in two concentrations; one 100 mg and the other 200mg, using three types of super disintegrants such as Crospovidone, Sodium starch glycolate, and Amberlite IRP88, respectively. From *in vitro* drug percentage release, it was shown that F6 formulation gives a good percentage of drug release compared to the rest of the formulation.

5. In Vivo Studies

5.1 *Vivo* pharmac\okinetic studies

Pharmacokinetic study was conducted on rats with Formulation F6 and the pure drug. The results for the Plasma concentration v/s time profile are shown in Figure 14, and the log plasma concentration v/s time as shown in Figure 15, pharmacokinetics parametres are shown in Table 17.

5.2 In-vivo pharmacokinetic analysis

Pharmacokinetic parametres were estimated by plotting the graph between the plasma concentration vs. time. After plotting the graph AUC, C_{max}, t_{max} was obtained by the same graph plot. Then, to determine the elimination rate, constant (K_{el}), the semi – logarithmic plot was plotted between the plasma concentration vs time. To calculate the elimination half–life $t_{1/2} = 0.693/K_{el}$., this formula was used. To statistically calculate AUC one-way, ANOVA was applied at 0.05 level intervals in the graph pad prism software version 5.01.[14] The results for the plasma concentration v/s time profile are shown in Figure 5 and the obtained pharmacokinetics parametres are shown in Table 6.

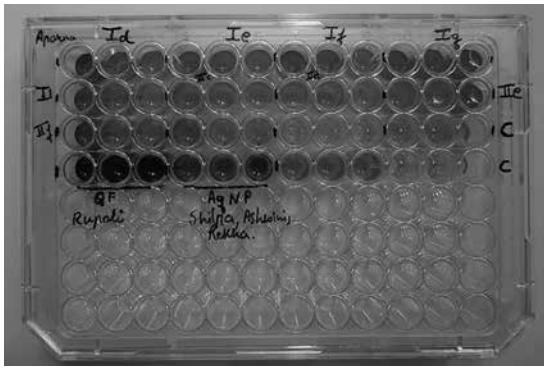

Figure 7: 96 well plates

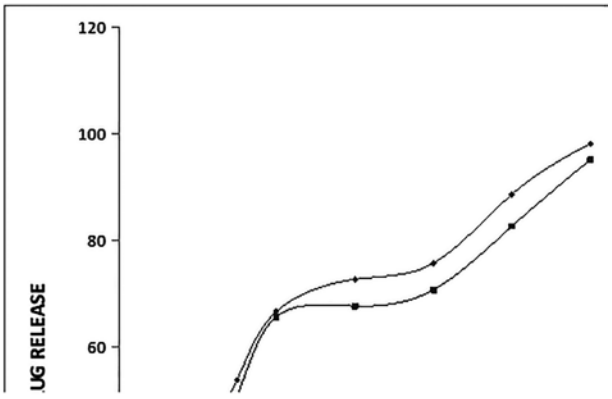

Figure 8: In vitro drug release study of F6 formulation before and after stability at 4°C.

Table 8: Pharmacokinetic parametres of Quercetin.

Pharmacokinetic parametres	Formulation F6
C_{max} (ng/ml)	100
T_{max} (minute)	10
AUC (ng/minute/ml)	633.66
K_{el}	0.178
$t_{1/2(hr^{-1})}$	4

5.3 In Vivo pharmacodynamic analysis

QF: Quercetin F6 Batch Formulation

IC50: Inhibiting Concentration

O.D: Optical Density

QF , IC50, O.D used in Table 9

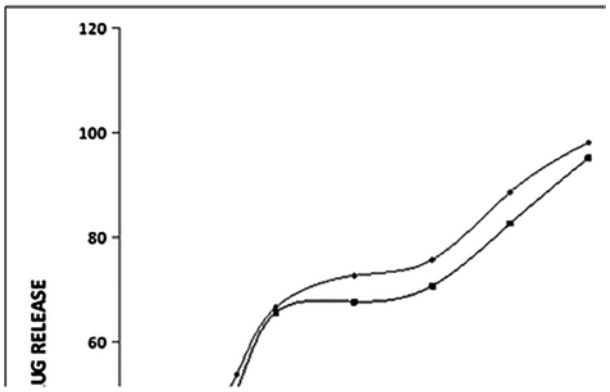

Figure 9: *In vitro* drug release study of F6 formulation before and after stability at 25°C.

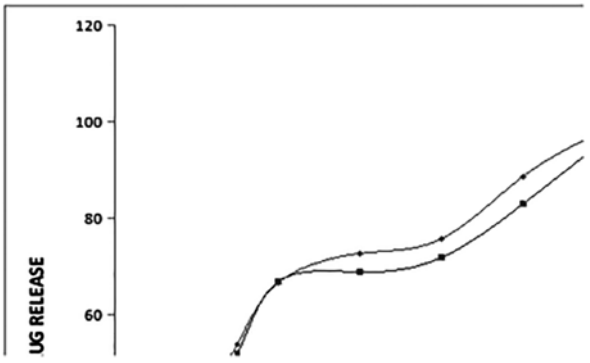

Figure 10: *In vitro* drug release study of F6 formulation before and after stability at 37°C.

6. Stability study

In this study, the accelerated stability studies for one month were conducted on the final optimized formulation (F6) as per the ICH guidelines at 4°C±2°C/60%RH ±5%, 25°C±2 °C/65%RH ±5 % and 37° C ±2°C/65%RH ±5%. After one month the tablets were withdrawn and analyzed for physical characterization it showed with changes in properties, reduction in drug content and reduction in *in vitro* drug release.

Table 9: In Vivo results of Quercetin dispersible tablet (Formulation F6) for anticancer activity.

Sr. No.	Compound	Concentration (µG)	O.D. at 492nm	% of cell lysis	IC50
1.	QF	10	3.004	100%	Very <10 µG
2.	QF	20	3.240	100%	
3.	QF	30	3.500	100%	
4.	Control	-	0.564	No lysis	-

Table 10: Stability studies – In Vitro release studies of selected formulation F6 % release at 4° C±2°C/60%RH ±5%, 25ºC± 2°C/65%RH ± 5% and 37°C±2°C/65%RH±5%.

Before Stability	Time In Minutes	%Release at 4° C ±2° C/60%RH ±5%	%Release at 25° C ±2° C/ 65%RH ± 5 %.	%Release at 37° C ±2° C/65%RH±5%
38.09	5	35.25	35.50	36.02
44.08	10	42.08	42.42	42.70
53.84	15	50.84	51.01	51.80
66.66	20	65.66	66.02	66.85
72.72	30	67.72	68.03	68.88
75.76	40	70.76	71.05	71.87
88.70	50	82.70	82.75	83.01
98.25	60	95.25	96.05	96.25

7. Conclusion

Oral dispersible tablets (ODT) of Quercetin were successfully prepared by using direct compression method. The various advantages of ODT will surely enhance the patient compliance, low dosing, and rapid onset of action, increased solubility due to complexation with soluplus, increased absorption of drug good stability. From this study, it can be concluded that the prepared dispersible tablets showed better disintegration and drug release of formulation F6 disintegrated within a few seconds; thereby enhancing absorption, and it shows anticancer activity in lung carcinoma

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