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RESEARCH ARTICLE

Development, Evaluation and *in vitro* Release Kinetics Study of Immediate Release Tablets of Quercetin Isolated from *Bauhinia acuminata* Leaves Extract

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Abstract

Objective: To isolate quercetin, a flavonoid, from leaves extract of *Bauhinia acuminata* and to formulate and evaluate immediate release tablets of this quercetin employing direct compression method. **Methods:** Quercetin was isolated by column chromatography and characterized by FTIR, ^{1}H and ^{13}C NMR. Next different formulation blends were prepared using the isolated quercetin with microcrystalline cellulose, magnesium stearate and sodium starch glycolate. Pre-compression studies were performed and tablets were prepared by direct compression method. Tablets were evaluated for various post formulation parameters including disintegration and *in vitro* dissolution. Release kinetics and release mechanism were also studied from different kinetics plots. **Finding :** The pre-compression parameters were within the range of hardness (3.37 $\pm$ 0.058 to 3.78 $\pm$ 0.058 kg/cm^2), weight variation (251.25 $\pm$ 5.38 to 251.45 $\pm$ 5.66 mg), friability (<1%), Drug content (98.17 $\pm$ 0.86 to 98.20 $\pm$ 0.99 %), disintegration (187.17 $\pm$ 2.48 to 126.5 $\pm$ 2.26 sec) and *in vitro* dissolution study (85.33 $\pm$ 0.95 % and 86.47 $\pm$ 0.70 %) within 30 minutes and 96.84 % and 98.19 %) within 1 hr respectively for F2 and F3. **Novelty:** Only few scientific reports are present for *Bauhinia acuminata* and majority of them are related to pharmacological properties of the extract from the plant only. Here in this study quercetin was isolated for the very first time from *Bauhinia acuminata* to the best of our knowledge and not only this, the isolated quercetin was formulated to immediate release tablet which is again being reported from this plant for the first time.

Keywords: Bauhinia acuminata; Immediate Release Tablet; Quercetin; Super Disintegrating Agents; Release Kinetics

1 Introduction

The genus "Bauhinia" has many different species under this but the majority of the works have been done with Bauhinia variegata or other species and most of these are

mainly pharmacological studies of extracts obtained from these plants [1,2]. *Bauhinia acuminata Linn.* (Caesalpiniaceae), unlike its counterparts has not been explored that much. Though few of the pharmacological properties such as antioxidant [3], anti-nociceptive, anti-tumour [4] etc. from different parts of the plant have been reported recently but the isolation and characterization of the phytoconstituents following their formulation and evaluation are neglected.

In this study an attempt was made to address this important research gap between studies of activities of extracts to the isolation of active compounds and development of suitable dosage form. The leaves of the plant were reported to contain alkaloids, phenols, glycosides and flavonoids [3]. In one of our previous study the presence of Quercetin in *Bauhinia acuminata* was indicated and quantified [5] and here to proceed further the present work aimed at the isolation of quercetin from leaves extract of *Bauhinia acuminata* Linn and to formulate and evaluate immediate release tablets with this isolated quercetin by direct compression technique using varying and very less amounts of super disintegrating agents followed by the evaluation of the tablets.

2 Methodology

2.1 Materials

All solvents of analytical grade were purchased from Merck (Mumbai, India). Microcrystalline cellulose, magnesium stearate, Sodium starch glycolate were obtained from Loba Chemie Pvt. Ltd (Mumbai). All other chemicals required in the study were purchased from Merck (Mumbai, India).

2.2 Collection and Identification of Plant material

The plant materials (Leaves) were collected from Barasat of North 24 Pgs in West Bengal, India was identified and authenticated from Botanical Survey of India, Howrah, India. A sample herbarium (BCDACPT/2015-16/01) is deposited in the Dept. of Pharmacognosy, BCDA College of Pharmacy & Technology, Barasat, India for future reference.

2.3 Preparation of the Leaves Extract

The plant material was shade dried and powdered. Required quantity of powdered material was macerated with methanol for 72 hours with occasional shaking. The extract was filtered and dried under reduced pressure to get the concentrated extract. This was kept in desiccator for 3 days to get fully dried extract powder [5].

2.4 Column Chromatography

The extract was subjected to systematic column chromatography using different solvent systems. Silica gel was used as the stationary phase in the Column chromatography to isolate constituents by gradient elution technique.

2.4.1 Column 1 (Fractionation)

The column was first eluted with 100% petroleum ether. The polarity of mobile phase was gradually increased with ethyl acetate and then methanol at 25% interval. Total 9 fractions were collected, named as C1-FBA1 to C1-FBA9, and dried in reduced pressure. All the fractions were subjected to TLC using Toluene, Ethyl acetate and Formic acid (5:4:0.2 v/v/v) as the mobile phase for the identification of the desired bands.

Based on the TLC study C1-FBA4 to C1-FBA8 (Pet ether : Ethyl acetate = 25:75, Ethyl acetate 100%, Ethyl acetate : Methanol = 75:25, 50:50, 25:75) were combined due to homogeneity and strong presence of flavonoids and further subjected to column chromatography to isolate the targeted compound.

2.4.2 Column 2 (Fractionation and Isolation)

The combined fractions was chromatographed again over a silica gel column using chloroform and methanol under gradient conditions at 10% interval to yield 11 sub-fractions which were named as C2-FBA1 to C2-FBA11. Based on the TLC study two fractions (C2-FBA3 and C2-FBA4) and three fractions (C2-FBA6 to C2-FBA8) were combined separately due to homogeneity and concentrated to one-fourth volume and kept overnight in the refrigerator. The combination of C2-FBA6 to C2-FBA8 yielded yellow coloured powder as ppt which was collected, filtered, washed with water and considered for further characterization.

2.5 Formulation of tablets

Different Pre-compression parameters were studied as follows.

2.5.1 Bulk Density

Bulk density is determined by a constant mass method using measuring cylinder. The bulk density of a powder is the ratio of the mass (m) of an untapped powder sample to its volume (V), including the contribution of the inter-particulate void volume. It is expressed in gm/ml and is given by m/V [6,7].

2.5.2 Tapped density

Taped volume is measured by taping measuring cylinder till there is no change in volume. It is expressed in gm/ml and is given by the following formula [6,7].

Tapped density = m/V_f

Where m = mass of the powder

V_f= Tapped Volume (Final volume after tapping in ml)

2.5.3 Hausner ratio and Compressibility index

The compressibility index or Carr's index and Hausner ratio are simple, fast and popular indirect parameters of predicting flow characteristics. The compressibility index and Hausner ratio were determined by measuring both the Bulk density and tapped density [6,7].

Hausner ratio = Tapped density /Bulk density

Compressibility index = 100 x {(tapped density – bulk density) / tapped density}

2.5.4 Angle of repose

This parameter measures the frictional forces in a loose powder. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Commonly it is determined by the fixed height method using a funnel. The angle of repose is calculated using the following formula [6,7].

$\tan \theta = h/r$

Angle of repose (θ) = $\tan^{-1}(h/r)$

Where, h = height of the powder pile

r = radius of pile circle

2.5.5 Absorption spectra of isolated quercetin

The absorption spectra were prepared using phosphate buffer pH 7.4 in the range of 200-400 nm.

2.5.6 Calibration curve of isolated quercetin

It was plotted by using UV spectrophotometer (Shimadzu 1700, Japan). For this it was dissolved in phosphate buffer pH 7.4 and diluted to form solution of different concentrations (2 – 20 μg/ml) and analyzed under UV spectrophotometer at the λmax 369 nm.

2.5.7 FTIR study

The infrared spectra (Bruker, Alpha II, ECO-ATR, Germany) were taken by KBr disk method for the isolated quercetin and other excipients like microcrystalline cellulose, magnesium stearate and sodium starch glycolate separately and of mixture of these.

2.5.8 Preparation of immediate release tablets of isolated quercetin

Three different formulations (F1, F2 and F3) of the isolated quercetin with different ratio of excipients were prepared. The excipients used were MCC, sodium starch glycolate and magnesium stearate. The amount of the isolated quercetin and magnesium stearate was fixed as 50 mg/tablet and 7.5 mg/tablet respectively in all the formulations. The amount of MCC in different formulations was 182.5, 177.5 and 172.5 mg/tablet respectively in F1, F2 and F3; whereas 10, 15 and 20 mg/tablet of sodium starch glycolate was used in F1, F2 and F3 respectively. The total weight of the single tablet was 250 mg. Next isolated quercetin was blended with diluents and then sodium starch glycolate were added, blended and the mixture thus obtained was ready for direct compression and compressed in tablet punching machine [8,9].

2.6 Post compression studies

2.6.1 Hardness and friability

The hardness and friability were determined using the Monsanto hardness tester (Cadmach, India) and the Roche friabilator (mvtex, India) and expressed in kg/cm^2 and % respectively[6,7].

2.6.2 Weight variation test

It was done as stated in earlier studies. 20 tablets were taken randomly, their individual weights noted, and it was compared with the average weight for the weight variations[6,7].

2.6.3 Drug content

Five tablets were powdered and drug equivalent to 50 mg powder was dissolved in buffer pH 7.4 and after appropriate dilution it was analyzed spectrophotometrically at 369 nm (Shimadzu 1700, Japan) and further calculated to determine drug content in each tablet[6,7].

2.6.4 Disintegration test

Disintegration was performed as stated earlier. Temperature was maintained at 37 °±2 °C and the apparatus (mvtex, India) was operated till each of the unit dosages come out from the basket[6,7].

2.6.5 In vitro drug release study

USP dissolution test apparatus (paddle type, Lab India DS 8000) was employed containing 900 ml of phosphate buffer pH 7.4 at 37±0.5^{0}C temperature and at 50 rpm for one hour. At every 10 minutes interval specified quantity of sample was withdrawn and further studied by UV Spectrophotometer at 369 nm[7,9].

2.6.6 Drug release kinetic study

The data obtained from the *in vitro* release study were analyzed using linear regression method according to the specified equations of zero order, first order, higuchi model, hixon-crowell model and korsmeyer-peppas model. Different plots were made such as cumulative % drug release vs. time (Zero order kinetic model); log cumulative of % drug remaining vs. time (First order kinetic model); cumulative % drug release vs. square root of time (Higuchi model); cube root of drug % remaining vs. time (Hixson-Crowell cube root law) and log cumulative % drug release vs. log time (Korsmeyer-Peppas model)[10,11].

3 Results and Discussion

3.1 Structure elucidation of isolated compound

The isolated compound was obtained as yellow powder, Melting point 314 – 317 °C.

UV-Vis (MeOH) λmax = 369 nm and 256 nm. LC/MS- ESI-MS m/z: 303.3 $[M+H]^+$.

FTIR spectra were obtained by Bruker, Alpha II, ECO-ATR (Germany) system at the range of 4000-400 cm-1. The FTIR spectrum (KBr, ν_{max}, cm^{-1}) of the isolated compound shows different characteristic bands as follows. 3408.84 and 3321.17 (OH, stretching), 1380.68 (OH, bending), 1665.09 (C=O aryl ketonic stretch), 1608.48, 1561.76, and 1520.60 (C=C aromatic stretch), 1316.61 (C–H aromatic in-plane bending), 936.48, 825.38, 685.80, and 602.11 (out-of-plane bending), 1260.31 (C–O stretching in the aryl ether ring), 1204.91 (C–O stretching in phenol), 1164.54 (C–CO–C stretch and bending in ketone).

NMR spectral studies for the isolated compound were carried out using Bruker Advance TM III 300 Spectrometer (Bruker Biospin, Germany) at 22 °C, 300 MHz using DMSO as solvent and TMS as an internal standard. The ^{1}H and ^{13}C NMR spectral data with their possible interpretation is given in Table 1 and the probable position of the data in the structure of the compound is given in Figure 1

Table 1. ^{1}H and ^{13}C NMR Spectral Data

Position[#]	^{1} H	d (ppm)	J (Hz)[##]	^{13} C	Carbon
1	-	-	-	161.42	-
2	1H	6.40	d, 2.0	98.67	CH
3	-	-	-	168.98	-
	OH	9.36	br	-	-

Continued on next page

Table 1 continued

4	1H	6.18	d, 2.0	103.47	CH
5	-	-	-	165.79	-
	OH	10.75	br	-	-
6	-	-	-	108.22	-
7	-	-	-	180.95	-
8	-	-	-	140.76	-
	OH	12.49	s	-	-
9	-	-	-	150.16	-
10	-	-	-	127.22	-
11	1H	7.67	d, 2.4	120.31	CH
12	-	-	-	152.15	-
	OH	9.36	br	-	-
13	-	-	-	152.79	-
	OH	9.36	br	-	-
14	1H	6.88	d, 8.4	120.83	CH
15	1H	7.54	dd, 8.4,2.0	125.39	CH

Refer Figure 1 for numbering
1H-1H multiplicity and coupling constants
s-singlet, d-doublet, dd-doublet of doublet, br-broad.

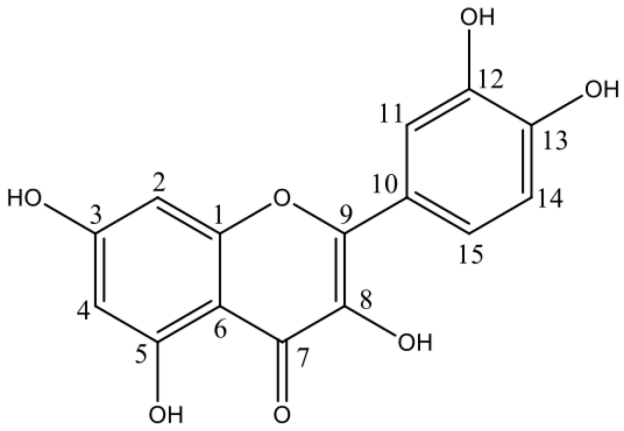

Fig 1. Probable position of the NMR data in the structure of the isolated compound (Numbers are used only to indicate NMR data)

Combination of all the spectral data indicated that the compound contains a flavonol skeleton bearing the molecular formula $C_{15}H_{10}O_7$ and it was identified as 2-(3′,4′-dihydroxy phenyl)-3,5,7-trihydroxy chromen- 4-one or Sophoretin or Quercetin. The findings were also agreed the available literature [12,13].

Quercetin, one of the most potent antioxidants, is usually found in some of the very common fruits and vegetables like apples, grapes, berries, tomatoes, onions, lettuce, kale, tea, saffron etc. [14]. Beside many of common applications, in recent years quercetin has been proved to be beneficial in Rheumatoid arthritis [15], management of Type 2 diabetes and its complications [16]. Even during COVID pandemic it was successfully tested for its antiviral properties against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and for the prophylaxis of the same [17,18].

Despite of having huge beneficial potential in pharmaceutical field, the number and extend of studies on formulation and evaluation of dosage forms of isolated quercetin is surprisingly very limited. Here in this study, to the best of our knowledge, quercetin has been isolated from *Bauhinia acuminata* for the very first time and formulated as immediate release tablets.

3.2 Formulation of Tablets

The immediate release tablets of the isolated quercetin were prepared and evaluated for various parameters. The drug - excipients compatibility study by FTIR confirms that the isolated compound was compatible with the other excipients used.

Results of different pre-compression studies are shown in Table 2 which indicated that the values were within the acceptable limits of the pharmacopoeial specification and the blends were having fare to poor flow property.

Table 2. Pre-compression studies

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index	Hausner ratio	Angle of repose
F1	0.3989 ± 0.001	0.5406 ± 0.003	26.1971 ±0.266	1.3550 ± 0.005	36.0313 ± 0.496
F2	0.4983 ± 0.001	0.6637 ± 0.004	24.9171 ±0.072	1.3319 ± 0.001	33.5448 ± 0.252
F3	0.6211 ± 0.004	0.7634 ± 0.006	18.6327 ±0.571	1.2290 ± 0.009	31.7401 ± 0.23

Values are expressed as Mean ± SD, n=3

The post compression evaluations results are shown in Table 3 which indicated that the values were within the range of pharmacopoeial standards.

Table 3. Post compression evaluations

Formulation	Hardness (Kg/Cm^2)*	Friability (%)	Weight variation*	Drug content (%)*	Disintegration (Sec)*
F1	3.7667 ± 0.06	0.3581	251.3 ± 4.95	98.1676 ± 0.88	187.1667 ± 2.48
F2	3.5667 ± 0.06	0.4573	251.45 ± 5.66	98.2037 ± 0.99	155.8333 ± 2.79
F3	3.3667 ± 0.06	0.6368	251.25 ± 5.38	98.1676 ± 0.86	126.5 ± 2.26

* Values are expressed as Mean ± SD, n=3

The data in hardness test suggested that the formulations possessed good mechanical strength. The weight variations (251.25 ± 5.38 to 251.45 ± 5.66 mg) and friability of all the formulations were also within the approved range (<1%). The results of drug content were in the range between 98.17 ± 0.86 to 98.20 ± 0.99 % which were within the limits. The Disintegration study results (187.17 ± 2.48 to 126.5 ± 2.26 sec) showed that the formulations were disintegrated faster with the increase in the concentration of super-disintegrants (from F1 to F3).

The *in vitro* dissolution study shown that except F1, the other two formulations (F2 and F3) were able to release more than 85% of drug (85.33 ± 0.95 % and 86.47 ± 0.70 % respectively for F2 and F3) within 30 minutes. The time taken to release 98.19 % drug for F3 was 1 hr, whereas in the same time F1 and F2 were able to release 93.09 % and 96.84 % drug respectively (Figure 2).

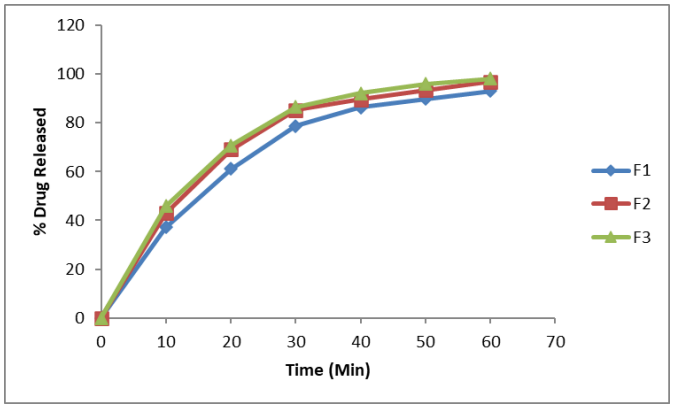

Fig 2. *In vitro* drug release profiles of formulations (F1, F2 and F3)

Immediate release tablets, as the name indicates, should release their active ingredients within very short period of time (≥85% of labeled amount of active medicament within 30 minutes) and hence these are prepared in such a way that when taken orally these are disintegrated instantaneously and release the drug without having any special rate controlling features like special coatings or other techniques [19]. The results of drug release in this study also indicated that out of three formulations tested, two of them (F2 and F3) released more than the specified amount and hence these were eligible to be called as immediate release formulations.

3.2.1 Drug Release Kinetics

Data obtained from *in vitro* drug release studies were plotted in various kinetic models and values are given in Table 4 . The best fitted release data was evaluated by coefficient of determination (R^2).

Table 4. *In vitro* drug release kinetics data of all formulations

Formulation	Zero order		First order		Higuchi		Hixon-Crowell		Korsmeyer-peppas		
	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	K_{KP}	R^2	n
F1	1.065	0.86	0.044	0.987	12.20	0.934	-0.022	0.812	1.1	0.95	1.0
F2	0.99	0.82	0.056	0.99	11.41	0.908	-0.019	0.78	1.22	0.93	0.89
F3	0.98	0.84	0.067	0.998	11.29	0.915	-0.018	0.792	1.26	0.94	0.85

Comparing the R^2 values of all the formulations First order and Higuchi model showed the better fitting of data. The first order produced greater correlation of all formulations (R^2=0.987 to 0.998 of) than all other models which indicated that the release of drug from the formulated tablets followed first order release kinetics that is the release is directly proportional to the concentration of the drug[10,11].

3.2.2 Mechanism of Drug Release

To evaluate the mechanism of drug release, the data of all the formulations were plotted in Korsmeyer-peppas model as log cumulative percentage of drug released vs log time, and the exponent "n" was calculated through the slope of the straight line.

For tablets, if the exponent n = 0.45, then the drug follows Fickian diffusion as its release mechanism and if 0.45< n<0.89, then it follows non-Fickian or anomalous diffusion. An exponent value of 0.89 or more than that indicates Case-II and super Case-II transport mechanisms[10,11,20].

In this study the corresponding plot indicated a good linearity in all the formulations (R^2 value 0.931 to 0.949). The release exponent "n" was found to be 0.85 and 0.89 (F3 and F2) which indicated that the drug release mechanism was perhaps controlled by more than one process, diffusion and erosion mechanisms, which is also termed as anomalous diffusion that is coupling of both[10,11,20].

The unique feature of this study was that the tablets were formulated using very less number of excipients and employing very simple technique as compared to the other available related studies. The final weight of the prepared tablets are also very less compared to the similar works making it cost more effective. In earlier studies quercetin was procured directly from the market[1,21,22] but here in this study Quercetin was isolated, characterized and used. The results also indicated that all the pre and post compression evaluation parameters were within the limits and based on the *in vitro* dissolution data F2 and F3 can also be successfully termed as immediate release formulations.

4 Conclusion

Natural drugs play an important role in modern medicine. However, studies on isolation of active medicinal phytoconstituents and thereafter formulation of such entities into any suitable dosage forms have always been in scanty. In this study an active constituent, Quercetin, was isolated from the leaves of *Bauhinia acuminata* and formulated as tablet dosage form for the very first time. All the formulations passed the different parameters specified in pharmacopoeia and as indicated in the results, it can be stated that the higher concentration of super disintegrating agent leads to the faster disintegration and release of drug. The mathematical data of the release study revealed that it was best fitted with first order kinetics and followed coupled diffusion and erosion mechanisms. All these findings lead the formulation to be an important and potential alternative in modern medicine. However, re-evaluation of data after large scale manufacturing and long term stability studies along with clinical trials are highly suggested as further studies for the development of these formulations.

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