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Research Article

Design and *In-vivo* Evaluation of Quercetin Nanosponges-based Buccal Tablets of Quercetin

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ABSTRACT

The objective was to increase the bioavailability of quercetin by creating a controlled release formulation using nanosponges based on cyclodextrin. Based on the early testing, a 3-factor, 3-level Box-Behnken design with quercetin was loaded into nanosponges using the freeze-drying process. The prepared nanosponges were examined after being described and made into tablets. The quercetin-loaded nanosponges have particle sizes ranging from 36.45 to 135.27 nm, encapsulation efficiencies ranging from 42.37 to 88.44%, and drug release percentages at 6 hours ranging from 53.04 to 82.64%. The FTIR, DSC, and XRD investigations validated the Quercetin interaction with nanosponges. The medicine released from the nanosponges buccal tablets *in-vitro* at a rate of 99.75%, and stability testing showed no significant changes within six months after the nanosponges were transformed into tablets. *In-vivo* studies in rats showed that quercetin optimised nanosponges tablets C_{max} of 6.27 ± 0.06 ng/mL was significantly higher ($p<0.05$) than the pure drug's C_{max} of 3.07 ± 0.086 ng /mL. Both the nanosponges tablet formulation and the pure drug suspension had T_{max} values of 4.0 ± 0.07 and 0.5 ± 0.08 h, respectively. The nanosponges tablet formulation had a greater $AUC_{0\text{-infinity}}$ (38.54 ± 0.65 ng.h/mL) than the pure drug suspension formulation 7.84 ± 1.08 ng.h/mL. In comparison to the pure drug, the nanosponges tablet formulation had a considerably greater $AUC_{0\text{-t}}$ ($p<0.05$). Poorly soluble quercetin tablets developed for regulated drug delivery showed enhanced complexing ability with increased bioavailability using cyclodextrin-based nanosponges.

INTRODUCTION

Quercetin (3,3',4',5,7-pentahydroxy-flavone) is the biggest flavonol subclass member among the various flavonoids identified to date. It has been proven to have anti cancer, anti oxidation, anti inflammation, reducing blood cholesterol, dilating coronary arteries, anti-platelet aggregation, anti anemia, and antianaphylaxis properties, among other biological and pharmacological actions.[1] However, due to its poor solubility, low hydrophilicity (log *p-value* of 1.81), gastrointestinal instability, significant first-pass metabolism, and minimal absorption in the gastrointestinal system, quercetin is a difficult chemical to deliver pharmaceutically. Quercetin is classified as BCS class II.[2] It dissolves in water at 7.7, and 5.5 lg/mL in simulated gastric fluid, and 28.9 lg/mL in simulated intestinal fluid (SIF). The oral bioavailability of the drug was shown to be less than 17% in rats and even less than 2% in humans, restricting its therapeutic use in traditional dose forms.[3] As a result, a better oral formulation of quercetin with enhanced bioavailability and activity is necessary. In light of the many drug delivery systems described in the literature, quercetin nanoparticulate formulation appears to be a viable option for improving solubility and stability at the same time. Nanosponges are recently developed hypercross-linked cyclodextrin polymers nanostructured to form three-dimensional networks; they are obtained by reacting cyclodextrin with a suitable crosslinking agent such as carbonyl diimidazole or diphenyl carbonate. Cyclodextrin-based nanosponges showed superior complexing ability than natural

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cyclodextrins toward many molecules. They have been used to increase the solubility of poorly soluble actives, to protect the labile groups, and to control the release.[4] Due to their unique physiological characteristics, buccal mucoadhesive dosage forms have been studied extensively over the last decade. The buccal route could be employed for both local and systemic administration. These formulations could be conveniently administered at disease sites, reducing potential side effects, improving patient compliance, and exhibiting long-term retention within the specific site of action. In the present study, we intended to develop nanosponges incorporated with buccal tablets of quercetin using cyclodextrin nanosponges as novel nanocarriers.

Materials And Methods

Materials

Quercetinwas obtained as a gift sample from MSN laboratories Pvt. Ltd, β-Cyclodextrin was obtained from Gangwal Chemicals Pvt. Ltd. (Mumbai, India)., Diphenyl carbonate, HPMC K100LV, Carbopol 934P purchased from Euclid Pharmaceuticals Limited, Mumbai, dimethyl sulfoxide and ethanol was purchased from Qualigens, Thermo Fisher Scientific India Ltd, Mumbai

Preparation of β-Cyclodextrin Nanosponges (NS)

Cyclodextrin based nanosponges were prepared in our laboratory using diphenylcarbonate for the crosslinking as reported elsewhere.[5] Five types of nanosponges were prepared using different molar ratios of reactants. The molar ratios and concentrations of both reactants were used as shown in Table 1.

Characterization of β-cyclodextrin Nanosponges

Characterization of the prepared β-cyclodextrin nanosponges for particle size, polydispersity index and zeta potential were analysed using a Mastersizer 2000 (Malvern Instruments Ltd, Worcestershire, UK).[6]

Fabrication of Quercetin-loaded β-Cyclodextrin Nanosponges

Quercetin loaded nanosponges were prepared by lyophilisation technique. In 500 mg of nanosponges were suspended in 100 mL of Milli Q water using a mechanical stirrer. To the above mixture 500 mg of quercetin was added and the mixture was sonicated for 20 minutes to prevent aggregation. After lyophilization the collected dry powder was stored in a desiccator.[7]

Design of Experiments

On the basis of Box-Behnken design model provided by Stat-Ease Design Expert® software V8.0.1, 17 model experiments were randomly arranged (Tables 2 and 3) [8]

Data Analysis

The relationship between the selected factors and responses was described quadratic model based on comparison of different statistical measures, including model *p-value*, multiple correlation coefficient (R2), adjusted R2 and coefficient of variation (CV) values. Quadratic model of each individual response parameter was evaluated using multiple regression analysis.[8]

Table 1: Molar ratios and concentrations of β- cyclodextrin and diphenyl carbonate

S. No.	*Type of NS*	*Molar ratio (β-CD: DPC)*	*Concentration of β-cyclodextrin (g)*	*Concentration of diphenyl carbonate (g)*
1	NS1	1:2	4.548	1.712
2	NS2	1:4	4.548	3.424
3	NS3	1:6	4.548	5.136
4	NS4	1:8	4.548	6.848
5	NS5	1:10	4.548	8.560

Optimization

The nanoformulation was prepared in triplicate under optimal conditions to verify the validity optimization technique.[9]

Characterization of Prepared Quercetin Nanosponges

Particle size, polydispersity index and zeta potential were determined as per the procedure adopted for β-cyclodextrin nanosponges. The formulations were analysed for FTIR, DSC, PXRD as per the procedure adopted in reference.[10]

Characterisation of Prepared Quercetin Nanosponges

The "percent drug payload" and "percent drug encapsulation efficiency" were calculated using the following equation 1 and 2.

$$\%\ \text{Drug pay load} = \frac{\text{Weight of drug encapsulated in NS formulation}}{\text{Weight of the NS formulation taken for analysis}} \times 100 \quad (1)$$

$$\%\ \text{Drug encapsulation efficiency} = \frac{\text{Weight of drug encapsulated in NSformulation}}{\text{Initial weight of the drug fed for loading}} \times 100 \quad (2)$$

Preparation of Quercetin Loaded Nanosponges Buccal Tablets

An accurately weighed quantities of quercetin loaded nanosponges corresponding to 100 mg quercetin and the calculated Avicel PH-102, which was added to attain 300 mg tablet, were mixed for 10 min using mortar and pestle after which the magnesium stearate (6 mg) was added and blended for another 2 minute. The final mixtures were compressed using a single punch tablet machine with 8 mm, round, flat-faced single punch.[11]

Evaluation of Tablet Formulation

Uniformity of weight, hardness test, friability test, drug content, *in-vitro* disintegration test.[11,12]

In-vitro Release Study of Quercetin

In-vitro release of drug from quercetin pure drug, quercetin NS powder and quercetin NS loaded tablets was performed using the type II USP dissolution apparatus.[12] The dissolution medium was 900 mL 0.1 N HCl for first 2 hours then replaced with phosphate buffer pH 6.8 at a speed of 50 rpm and a temperature of 37 ± 0.5°C. The samples were withdrawn at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours. Equal amount of the fresh dissolution medium, retained at the same temperature, was immediately replaced. The samples were suitably diluted and analyzed using UC- spectrophotometer at 369 nm. The dissolution experiments were conducted in triplicate.

Short Term Stability Studies

Stability studies of the optimized formulation was carried out according to ICH guidelines. The stability of Quercetin buccal tablets was estimated after filling and sealing in light protective amber-colored bottles with rubber caps and aluminum covering. These were stored at three different temperatures and relative humidity (i.e., 25 ± 2°C, 60% ± 5; 30 ± 2°C, 65% ± 5; and 40 ± 2°C, 65% ± 5) and were inspected visually and the samples were withdrawn at specified time points and were examined for appearance, hardness, disintegration time, dissolution, and drug content.

Pharmacokinetic Studies of Quercetin

Animal Preparation

Healthy male wistar rats were (weighing 200–220 g) selected for this study, all the animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (temperature 25°C, relative humidity 45% and 12 hours alternate light and dark cycle) with 100% fresh air exchange in animal rooms, uninterrupted power and water supply. Rats were fed with a standard diet and *water ad libitum.* The institutional animal ethics committee approved the protocol of animal study (IAEC NO: 1447/PO/Re/S/11/CPCSEA-60/A).

Study Design

Rats were divided in to three groups at random containing 6 animals. The groups under treatment were designed as follows. group I: Pure quercetin drug solution group II: Quercetin nanosponges buccal tablets optimized formulation group III: Treatment control. The rats were fasted for 24 hours prior to the experiments. After 4 hours of dosing, foods were reoffered. Rats were anesthetized by i.p. injection of 1.2 mL of a 25% (w/v) urethane solution in saline and fixed on their back. Before buccal administration, a blank blood sample (0.3 mL) was taken. After a tablet was administered to the right cheek mucosa of every rat, 0.1 mL saline was placed in the mucosa near the bottom of the inserted tablet, and the tablet was gently pressed into the mucosa to fix it to the mucosal surface at the administered site. Blood samples (0.3 mL) were withdrawn via the jugular vein at appropriate time points. Plasma was obtained by centrifugation of the blood at 1400X g for 5 minutes. Plasma (0.1 mL) was mixed with 0.1 mL of 1 M carbonate buffer (pH 9.5) and stirred vigorously. Then, 0.5 mL ethyl acetate was added, shaken vigorously, centrifuged at 1500 x g for 10 minutes, and frozen at –20°C until analysis.[13]

Determination of Quercetin in Rat Plasma by HPLC method

The Shimadzu LC 20A HPLC system (Maryland, USA) consists of an auto-sampler, a degasser, a binary pump, a model SPD-20A photodiode array detector and a model RF10AXL fluorescence detector. The chromatographic analysis was performed using the Supelcosil LC-18T C18 column (4.6 × 250 mm I.D.) with a particle size of 5 µm and was kept at 40°C. The isocratic mobile phase consisted of 0.3% trichloroacetic acid in water and acetonitrile HPLC grade (50:50, v/v) run at a 0.9 mL/min flow rate for 13 minutes The absorbance of quercetin was detected at 254 nm.[14] The applied conditions lead to good separation of internal standard thymoquinone (TQ) and quercetin with well-resolved peaks at retention times of 4.41 and 11.15 minutes, respectively.

Results and Discussion

Five types of nanosponges were prepared using different molar ratios of reactants.[15] The percent practical yield, Particle size, polydispersity index and zeta potential were measured and are as presented in Table 4. From the trials, the range of polymer to cross-linker ratio (0.2-0.8), stirring speed (2000–5000 rpm) and stirring time (350–550 minutes) were identified. Based on the initial results, a Box-Behnken design was employed to optimize the influencing variables.[15]

Mean Particle Size

Particle size of the nanoformulation ranges from 36.45–135.27 nm.[16] The interactive effect of AB on particle size at a constant level of C is as shown in Figs. 1a and b.

Encapsulation Efficiency

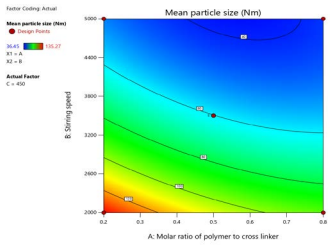
The encapsulation efficiency of nanosponges was found to be in the range of 42.37 to 88.44% (Table 2). The interactive effect of BC on encapsulation efficiency at constant level of A is as shown in Figs. 2a and b.

Percent Drug Release at 6 h

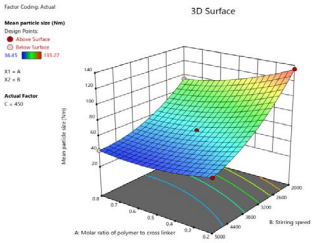
Percent drug release at 6h is an important measure to assess nanosponges' ability to control the drug's release for a desired period. Percent drug release from the nanoformulation ranges from 53.04 to 82.64% (Table 2). The polynomial model showed that only the variable

Table 2: BBD with list of dependent and independent variables with their respective levels and goals

Independent variables			*Levels*		
Variable		*Units*	*Low*	*Intermediate*	*High*
A	Molar ratio of polymer to cross linker		0.2	0.5	0.8
B	Stirring speed	rpm	2000	3500	5000
C	Stirring time	Min	350	450	550
Dependent variables			*Goal*		
Y1	Mean particle size	Nm	Minimize		
Y2	Encapsulation efficiecny	%	Maximize		
Y3	Percent drug release at 6h	%	Minimize		



(a)



(b)

Fig. 1: (a) 2D- Contour plot showing the interactive effect of A and B on mean particle size at constant level of C. (b). 3D- response surface plot showing the interactive effect of A and B on mean particle size at constant level of C.

A (Molar ratio) significantly affected the percent drug release from nanosponges.

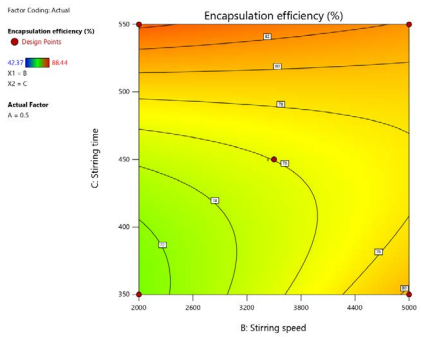
The effect of variable A on Y3 was described by using a perturbation plot (Fig. 3).

Optimization

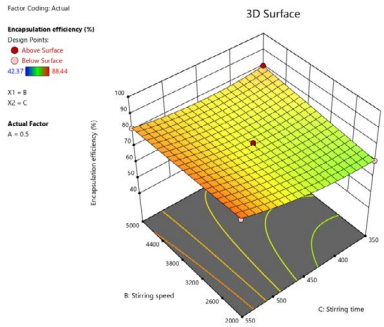
Derringer's desirability function (D) was used to optimize the selected variables which influence the response parameters. (Table 5).[17]

Morphology and Sizes of the Quercetin-loaded Nanosponges

The particle size analysis of quercetin loaded nanosponges revealed that the average particle size measured by laser light scattering method is around 40 to 50 nm with low polydispersity index. The particle size distribution



(a)



(b)

Fig. 2: (a) 3D- Contour plot showing the interactive effect of B and C on encapsulation efficiency at constant level of A. (b). 3D- response surface plot showing the interactive effect of B and C on encapsulation efficiency at constant level of A.

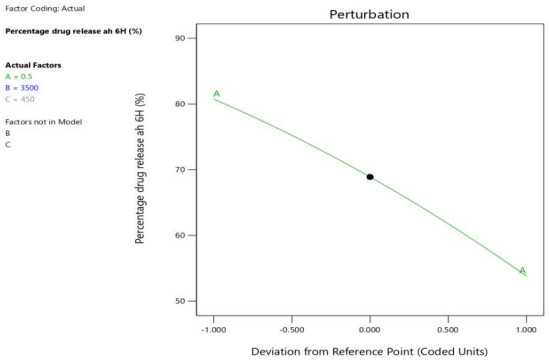


Fig. 3: Two-dimensional Perturbation plot- Effect of A on percent drug release at 6h

is unimodal and narrow, as seen in Table 6. A narrow polydispersity index means that the colloidal particles are homogenous in nature. A sufficiently high zeta potential indicates that the complexes would be stable and the tendency to agglomerate would be miniscule. The entire formulations prepared were found to be fine and free-flowing powders. The percent drug loading and encapsulation efficiency of prepared quercetin nanosponges were determined and are presented in Table 6.

Table 3: Observed responses of trial experiments as per BBD

Expt	*Molar ratio of polymer to cross linker*	*Stirring speed (rpm)*	*Stirring time (min)*	*Mean particle size (nm)*	*Encapsulation efficiecny (%)*	*Percent drug release at 6h (%)*
1	0.5	3500	450	68.25	90.82	60.28
2	0.2	5000	450	60.02	57.12	79.82
3	0.5	3500	450	69.49	90.18	60.92
4	0.5	5000	350	68.37	86.32	62.22
5	0.2	3500	550	63.14	57.88	79.12
6	0.5	2000	350	153.2	84.23	68.23
7	0.5	5000	550	52.27	93.21	60.54
8	0.5	2000	550	147.38	89.74	65.69
9	0.2	2000	450	153.42	53.44	83.11
10	0.8	2000	450	155.28	76.54	55.18
11	0.8	3500	550	81.77	79.82	54.11
12	0.5	3500	450	73.65	91.34	59.86
13	0.8	3500	350	79.21	76.56	54.45
14	0.8	5000	450	62.84	75.12	52.34
15	0.5	3500	450	69.33	90.88	59.76
16	0.5	3500	450	70.9	91.86	60.34
17	0.2	3500	350	89.68	54.13	81.05

Table 4: The percent practical yield, particle size, polydispersity index and zeta potential of different nanosponges

S. NO.	*Type of NS*	*Molar ratio (β-CD: DPC)*	*Practical yield (%)*	*Mean particle size (nm)*	*Polydispersity index*	*Zeta potential*
1	NS1	1:2	77.64 ± 2.76	111.96 ± 3.52	0.251 ± 0.005	-22.64 ± 2.12
2	NS2	1:4	82.27 ± 1.98	107.21 ± 4.88	0.308 ± 0.005	-25.16 ± 1.13
3	NS3	1:6	85.82 ± 3.12	115.67 ± 3.42	0.262 ± 0.005	-26.38 ± 3.24
4	NS4	1:8	90.35 ± 2.44	120.28 ± 4.26	0.418 ± 0.005	-23.02 ± 1.74
5	NS5	1:10	92.48 ± 1.89	99.33 ± 2.48	0.270 ± 0.005	-22.48 ± 1.46

(All determinations were performed in triplicate and values were expressed as mean ± S.D.,n = 3 ($p < 0.05$)

Table 5: Optimum conditions attained by applying restrictions on response parameters

		Predicted values				*Actual values*		
Independent variables	*Optimized values*	*Mean particle size (Y_1) Nm*	*Encapsulation efficiency (Y_2) %*	*Percent drug release at 6h (Y_3)*	*Batch*	*Mean particle size (Y_1) nm*	*Encapsulation efficiency (Y_2) %*	*Percent drug release at 6h (Y_3)*
Molar ratio of polymer to cross linker	0.80	36.831	85.991	53.813	F1	40.62 ± 4.62	87.06 ± 1.67	55.50 ± 1.28
Stirring speed	5000				F2	46.39 ± 4.19	86.27 ± 2.49	56.04 ± 2.17
					F3	48.21 ± 2.50	87.60 ± 1.28	56.75 ± 1.05
Stirring time	525 min							

n = 3 ($p < 0.05$)

Characterization of Cyclodextrin Nanosponges

FTIR and DSC studies confirmed no significant interactions, the formation of inclusion complex of quercetin with nanosponges and losing all its crystallinity which was confirmed by XRPD study.[18]

Preparation of Quercetin Loaded Nanosponges Buccal Tablets.

The mean weight ranged from 300.46 ± 2.27 to 301.97 ± 3.56 mg. The mean thickness ranges from 4.95 ± 0.46 to 5.19 ± 0.31 mm. The mean hardness ranges from 5.31 ± 0.38 to 5.45 ± 0.49 kg/cm^2. The mean friability values range from 0.51 ± 0.24 to 0.79% ± 0.18 and the average percentage drug content ranges from 98.84% ± 1.76 to 99.61 ± 1.19, as shown in Table 7.[19, 20]

T2 was discovered to have the greatest swelling index (Table 8). The surface pH values ranged from 6.5 to 6.6, indicating that all of the formulations give an acceptable pH in the salivary pH range of 5 to 7. (Table 9).[21]

Buccal pills had mucoadhesion of 19.26, 20.46, and 22.95 g, respectively (Table 9). Buccal tablet residence times varied from 6.4 to 6.7 hours, indicating that buccal tablets take this long to remove from the buccal mucosa.

In-vitro Release Study

The dissolution profiles of pure drug suspension quercetin and from different formulations of quercetin nanosponges powder and quercetin nanosponges buccal tablet (Fig. 4). A biphasic release pattern of quercetin from the prepared nanosponges buccal tablets was observed. The initial burst release was ranged from 17.64% of drug within 1-hour, followed by sustained release of the drug for 24 hours. The percent of quercetin released from nanosponges buccal tablets after 24 hours was 99.75%.[22, 23]

Short Term Stability Studies

The stability study's results indicated that there was no significant change in the visual appearance, hardness, disintegration time, dissolution and drug content, as shown in Table 10.[24,25]

Pharmacokinetic Parameters Comparison for Pure Quercetin Drug and Optimized Nanosponges Buccal Tablets

Fig. 5 indicates plasma concentration–time curve recorded post single oral dose of quercetin optimized nanosponges buccal tablets formulation in comparison to quercetin pure drug suspension.

C_{max} of the quercetin optimized nanosponges buccal tablets 6.27 ± 0.06 ng/mL was significant ($p<0.05$) as compared to the pure drug suspension formulation 3.07 ± 0.086 ng/mL. T_{max} of optimized nanosponges buccal tablet formulation and pure drug was 4.0 ± 0.07 and 0.5 ± 0.08 hours, respectively. $AUC_{0-\infty}$ infinity for quercetin optimized nanosponges buccal tablets formulation was higher (38.54 ± 0.65 ng.h/mL) than the pure drug suspension 7.84 ± 1.08 ng.h/mL. Statistically, AUC_{0-t} of the optimised nanosponges buccal tablet formulation was significantly higher ($p<0.05$) than pure drug suspension formulation. (Table 11).

Table 6: Particle Size, polydispersity index and zeta potential of plain nanosponges and drug loaded nanosponge formulation

Sample	*Mean particle size ± SD (nm)*	*Polydispersity Index*	*Zeta potential (mV)*	*Drug pay load*	*Encapsulation efficiency*
Plain NS	108.24 ± 3.67	0.30 ± 0.005	-21.37 ± 1.12	-	-
F1	41.36 ± 4.32	0.44 ± 0.005	-20.7 ± 1.62	48.15	87.88 ± 1.08
F2	46.9 ± 3.72	0.12 ± 0.005	-23.04 ± 1.74	49.37	86.73 ± 1.65
F3	48.72 ± 4.51	0.32 ± 0.005	-24.68 ± 1.19	48.02	87.64 ± 3.27

n = 3 ($p < 0.05$)

Table 7: Evaluation parameters of quercetin tablets

Formulation	*Weight (mg)*	*Thickness (mm)*	*Hardness (kg/cm^2)*	*Friability (%)*	*Drug content (%)*
T1	300.46 ± 2.27	4.95 ± 0.46	5.31 ± 0.38	0.51 ± 0.24	98.84 ± 1.76
T2	301.97 ± 3.56	5.06 ± 0.77	5.45 ± 0.49	0.67 ± 0.52	99.61 ± 1.19
T3	300.62 ± 4.27	5.19 ± 0.31	5.38 ± 1.32	0.79 ± 0.18	99.22 ± 2.61

n = 3 ($p < 0.05$)

Table 8: Swelling index of quercetin nanosponges loaded buccal tablet

Formulation no	*Time (hours)*					
	1	*2*	*3*	*4*	*5*	*6*
T1	50.62	52.91	59.88	61.81	65.75	68.21
T2	65.21	68.65	71.22	74.38	78.60	84.64
T3	52.34	55.29	58.69	62.26	69.27	71.49

n = 3 ($p < 0.05$)

Table 9: Surface pH, Mucoadhesive strength and *ex-vivo* residence time of quercetin nanosponges loaded buccal tablet

Formulation code	*Surface pH*	*Mucoadhesive strength (g)*	*Ex-vivo residence (hours)*
T1	6.6 ± 0.02	19.26 ± 0.62	6.4 ± 0.72
T2	6.5 ± 0.04	20.46 ± 0.76	6.5 ± 0.33
T3	6.6 ± 0.06	22.95 ± 0.27	6.7 ± 0.85

n = 3 ($p < 0.05$)

Table 10: Results of stability studies of the quercetin tablets (T2)

Condition	Days	Appearance	Hardness	Percent dissolution	Drug content
	0	White	5.45 ± 0.49	99.75 ± 4.99	99.61 ± 1.19
25 ± 2°C, 60% ± 5% RH	90	White	5.22 ± 0.67	99.66 ± 0.88	99.55 ± 0.74
	180	White	5.07 ± 0.46	99.52 ± 2.32	99.41 ± 0.63
	0	White	5.45 ± 0.49	99.75 ± 4.99	99.61 ± 1.19
30 ± 2°C, 65% ± 5	90	White	5.31 ± 0.56	99.68 ± 3.16	99.52 ± 0.76
	80	White	5.06 ± 0.34	99.59 ± 2.98	99.41 ± 0.69
	0	White	5.45 ± 0.49	99.75 ± 4.99	99.61 ± 1.19
40 ± 2°C, 75% ± 5	90	White	4.66 ± 0.18	99.69 ± 0.44	99.52 ± 0.59
	180	White	4.54 ± 0.20	99.65 ± 1.75	99.43 ± 0.15

n = 3 ($p < 0.05$)

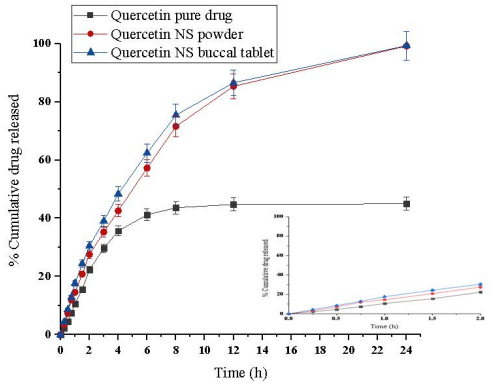


Fig. 4: *In-vitro* release of Quercetinpure drug, quercetin NS powder and quercetin NS buccal tablet [n = 3 ($p < 0.05$)]

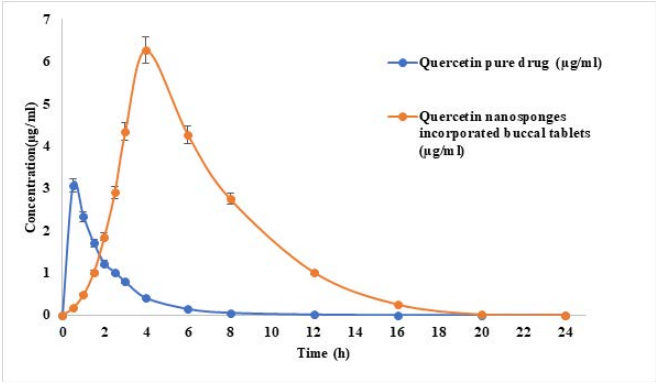


Fig. 5: Plasma concentration profiles of quercetin optimised nanosponges buccal tablets and pure drug

Table 11: Pharmacokinetic Parameters of quercetin optimized nanosponges buccal tablets formulation and pure drug

Pharmacokinetic parameters	*Quercetin pure drug*	*Quercetin optimized nanosponges buccal tablets*
C_{max} (µg/mL)	3.07 ± 0.086	6.27 ± 0.06
AUC_{0-t} (µg.h/mL)	6.3275 ± 1.27	37.61 ± 2.28
AUC_{0-inf} (µg.h/mL)	7.84 ± 1.08	38.54 ± 0.65
T_{max}(h)	0.5 ± 0.08	4.0 ± 0.07
$t_{1/2}$ (h)	11.129 ± 1.68	15.41 ± 1.46

In this study, quercetin-loaded nanosponges were made using the freeze-drying method. FTIR, DSC, and XRD investigations verified that using nanosponges resulted in forming a quercetin inclusion complex. The dissolution of the quercetin nanosponges was substantially higher than that of the pure drug due to the reduced drug particle size, the induction of a high-energy amorphous state, and intermolecular hydrogen bonding. Compared to pure quercetin, quercetin nanosponges buccal tablets had a 99% relative dissolving rate. The nanosponges' tablet Cmax of 6.27 ± 0.06 ng/mL was much greater ($p<0.05$) than the pure drug's C_{max} of 3.07 ± 0.086 ng/mL. Both the nanosponges tablet formulation and the pure drug had T_{max} of 4.0 ± 0.07 and 0.5 ± 0.08 h, respectively. The nanosponges tablet formulation had a higher $AUC_{0-\infty}$ (38.54 ± 0.65 ng.h/mL) than the pure drug suspension formulation 7.84 ± 1.08 ng.h/mL. In comparison to the pure drug, higher drug concentrations in the blood showed better systemic absorption of quercetin from nanosponges buccal tablet formulation.

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