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DESIGN, DEVELOPMENT AND CHARACTERIZATION OF SOLID DISPERSION OF QUERCITIN LOADED ORAL WAFERS

Sanjay Srivastava [1] and Akash Ved [*2]

Department of Pharmacy [1], Bhagwant University, Ajmer - 305004, Rajasthan, India.
Goel Institute of Pharmaceutical Sciences [2], Near Indra Canal, Ayodhya (Faizabad) Road, Lucknow - 226028, Uttar Pradesh, India.

Keywords:

Quercetin, Oral wafers, Solid dispersion, Solubility, Dissolution, Solvent casting

Correspondence to Author:
Dr. Akash Ved

Director,
Goel Institute of Pharmaceutical Sciences, Near Indra Canal, Ayodhya (Faizabad) Road, Lucknow - 226028, Uttar Pradesh, India.

E-mail: akashved@gmail.com

ABSTRACT: Quercetin (3, 3′, 4′, 5, 7-pentahydroxyl-flavone) is a flavonol, belonging to the class of plant secondary metabolites known as flavonoids. Quercetin and its derivatives have various beneficial effects against ailments like inflammation, oxidative stress, and cancer. The present research work aimed to prepare and characterize quercetin's solid dispersion (SD) to enhance solubility and thereby dissolution profile and further incorporate it into oral wafers. The solvent evaporation method was used to prepare solid dispersions using the polymer polyethylene glycol 6000 and pluronic F127. The drug and polymers were compatible, as evident from the FTIR data. The optimized batch was further evaluated by FTIR, DSC, PXRD & SEM. Wafers were prepared by solvent casting method using HPMC (5 & 15 cps), PVA, and plasticizer PEG (200,400) and propylene glycol. Quercitin-loaded SD was added to the polymer solution during casting. Highest drug release of 82.96 ± 1.76 % in 240 min was obtained with a drug to carrier ratio (1:1.5). It followed Higuchi's model when the amount of solvent was 20 ml. The drug was uniformly dispersed in the carrier, and crystallinity was significantly reduced as reflected in DSC, PXRD, and SEM results. The prepared SD showed a significant increase in solubility and dissolution profile. The data evidenced that the optimum amount of solvent was critical in modulating release rates. Hence, this strategy could be a promising option for the enhancement of solubility as well as dissolution profiles of quercetin.

INTRODUCTION: Quercetin (3, 3′, 4′, 5, 7-pentahydroxyl-flavone) is a flavone, belonging to a class of plant secondary metabolites known as flavonoids [1]. It is one of the six subclasses of flavonoid compounds [2].

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Numerous literature has reported biological and pharmacological activities, such as dilation in coronary arteries, lowering blood lipid, aggregation of anti-platelets, anti-cancer, anti-oxidative, anti-anemic, anti-inflammatory, and anti-anaphylaxis actions [3, 4].

It has the potential to inhibit the progression of carcinoma of the lung, colon, prostate and pancreas. It causes induction of cells differentiation and promotes cells apoptosis [2, 5]. It is assumed that the observed protective effects derive from the anti-

oxidative and radical scavenging capacity that quercetin shows in many *in-vitro* experiments [6]. Following 14C-quercetin doses given by oral as well as intravenous route, the data showed a large recovery of quercetin which strongly suggests that quercetin has extensive metabolism with a half-life of 23.1 h at room temperature [17-18]. Quercetin has very poor bioavailability and is dependent on the type and position of sugar moieties [19]. The bioavailability of the aglycone quercetin is, very poor. No free quercetin could be detected in human plasma after oral intake of high amounts of quercetin [8]. However, quercetin is having low hydrophilicity with minimal absorption in the gastrointestinal tract [8] with less than 17% oral bioavailability in rats and even 1% in men [20]. The absorption of quercetin is solubility and dissolution rate-limited [21-22].

Thus, new dosage forms of quercetin should be designed to address solubility and bioavailability to overcome these defects. The pharmacokinetic studies have shown that the dissolution rate of such drugs may be improved by decreasing crystallinity, bringing the particle size to nanoscale, producing high energy amorphous form, using an inclusion compound such as cyclodextrins [25]. Solubility and, later on, bioavailability [22] of quercitin can be improved by delivering it in prodrugs, nanocrystals, emulsions, liposomes, phospholipid formulations, polymer nanoparticles (PNs), micelles, and solid dispersions.

Among the several techniques reported in the literature, Solid Dispersion (SD) is one such reliable technique to improve the dissolution of poorly soluble drugs. Keeping in view the flexibility and comfort of patients, orally dissolving films, also known as oral wafers, are the most advanced form of the oral solid dosage form. The drug gets dissolved within a minute in the oral cavity without the need for water and chews after administration. Anatomically oral mucosa is 4–1000 times more permeable than the skin, resulting in quick absorption and instant bioavailability of drugs. After their application onto the tongue, it is almost impossible to spit them out because of their fast-dissolving behavior and adherence onto the mucosa. The objective of the present research work was to develop and characterize quercitin SD-loaded oral films to enhance quercitin oral BA.

MATERIALS AND METHODS:

Materials: Quercetin was purchased from SRL Chemicals Company (India). The surfactants pluronic F 127 (PF 127) and pluronic F 68 (PF 68) was purchased from Sigma-Aldrich (India). Polyethylene glycol 6000 (PEG 6000) and ethanol were obtained from SD fine (India). The solvent evaporation method was employed for preparing the solid dispersions. HPMC (5cps), HPMC (15cps), PVA, xanthan gum, PEG (200), PEG (400), propylene glycol, glycerin, mannitol, and aspartame were of analytical grades.

Drug-Excipient Interaction Studies through FTIR: The interaction between the drug & the polymers was studied by FTIR (Perkin Elmer Spectrum, version 10.03.06). The spectrum was executed in the scanning range of 450-4000 cm^{1}. The separate IR spectra of quercitin, polymers, and drug-polymer mixture were obtained.

Drug-Excipient Interaction Studies through TLC: The drug and polymer mixture was dissolved in methanol, and the mobile phase was prepared by taking solvents in the following ratio (Toluene: ethyl acetate: methanol: glacial acetic acid) (7: 2: 1: 0.1 v/v/v/v). The spot was observed under a UV lamp [8, 9].

Preparation of Solid Dispersion: The solvent evaporation method was used to prepare SD of quercetin with PEG 6000 (hydrophilic carrier) and pluronic F 127 (surfactant). A weighted quantity of PEG 6000 and PF 127(2% w/w) was taken in a beaker and dissolved in the required volume of ethanol with continuous stirring to obtain a clear solution with slight heating.

Weighed quantity of quercetin was then added stirring was continued for 10 more min. Evaporation of solvent was achieved by transferring the solution to a round-bottomed flask and using rota vapor (Ika, RV-10 digital) with operating conditions of 50°C, 60 rpm for 30 min. The recovered solvent can be further utilized for other batches. The solvent thus recovered was used for the preparation of the next batch. After one-day product can be scrapped from the round-bottomed flask which was kept overnight in a desiccator. The collected SD was stored in a desiccator for [24] and subjected to different characterization tests:

The Percentage Yield was calculated by:

$$\% \text{ yield} = (A/ B + C) * 100$$

Whereas, A = weight of solid dispersion, B = weight of polymers & C is the weight of the drug is taken.

Drug Content: Drug content was estimated using the UV method. The weighted sample from prepared formulations was dissolved in the solvent, passed through a syringe filter, and analyzed through a UV spectrophotometer (UV 1800, Shimadzu).

Drug content was determined by using the formula given below [24].

$$\% \text{ Drug content} = \text{Actual concentration of drug} / \text{Theoretical concentration} \times 100$$

Estimation of Solubility: Solubility analysis was carried out using the equilibrium solubility method described by Miller *et al*. 2012 [26].

***In-vitro* Dissolution Rate Studies:** *In-vitro* dissolution rate studies were performed per method.

TABLE 1: FORMULATION DEVELOPMENT OF ORAL WAFERS (F1-F9) USING VARIOUS POLYMERS

Ingredients	Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC (5cps)	91.66mg	91.66mg	91.66mg	-	-	-	-	-	-
HPMC (15cps)	-	-	-	91.66mg	91.66mg	91.66mg	-	-	-
PVA	-	-	-	-	-	-	91.66mg	91.66mg	91.66mg
PEG 200	0.05ml	-	-	0.05ml	-	-	0.05ml	-	-
PEG 400	-	0.05ml	-	-	0.05ml	-	-	0.05ml	-
Propylene Glycol	-	-	0.054ml	-	-	0.054ml	-	-	0.054ml
Glycerine	0.05ml	0.05ml	0.05ml	0.05ml	0.05ml	0.05ml	0.05ml	0.05ml	0.05ml
Mannitol	20.83 mg	20.83 mg	20.83 mg	20.83 mg	20.83mg	20.83Mg	20.83 mg	20.83 mg	20.83 mg
Aspartame	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Ethanol	0.83ml	0.83ml	0.83ml	0.83ml	0.83ml	0.83ml	0.83ml	0.83ml	0.83ml
Water	3.33ml	3.33ml	3.33ml	3.33ml	3.33ml	3.33ml	3.33ml	3.33ml	3.33ml

Trials Run for Screening of Polymers: Many polymers were used in the trial to test their film-forming property. Weighed quantities of different excipients as per the formulation table were dissolved in the distilled water and stirred for 3 h. To remove the entrapped air bubbles it was sonicated. The resulting solution was cast on a suitable inert platform and air-dried. Dried films were tested for clarity, surface appearance, stickiness, disintegration and folding endurance.

Preparation of Quercitin SD Loaded Oral Wafers: The modified solvent-casting method was used for preparing oral wafers. Polymers were dissolved in distilled water, and stirring was continued for 3 h and kept for 1 h to remove entrapped air bubbles. Weighed quantity of plasticizer, disintegrant was dissolved in ethanol (50%v/v); added sweetening agent in it with constant stirring for 45 min along with gentle heating to dissolve aspartame. Quercitin SD was added to a cooling solution.

After mixing both the phases, the resulting solution was cast on a suitable inert platform, and it was air-dried. The dried wafers were cut into desired sizes required for testing and stored at 25 °C [10, 11].

Characterization Ruercitin SD Loaded Fast Dissolving Wafers:

Visual Inspection: Prepared films were observed for properties like homogeneity, surface, color, and transparency.

Surface pH Determination: Wafers were moistened with 1 ml of phosphate buffer and kept for 30 s in a petri dish. This study was done on three films of each formulation, and mean ± SD was calculated [17].

Weight Variation: Randomly selected three films of 2.5 X 2.5 cm^2 size were weighed individually on a digital balance, and the mean weights ± S.D was calculated for each batch [16].

Film Thickness: A micrometer screw gauge (Popular science apparatus workshops, India) was used to measure the wafer at five positions (central and the four corners), and the mean thickness was calculated.

Tensile Strength: Universal testing apparatus (Scientific international, India) used a load cell of 1000 N for the tensile test. Tensile strain at break (%) and tensile stress at break (MPa) was calculated [12].

Percentage Elongation: The percentage elongation was measured by using the universal testing machine. It consists of two load cell grips. The lower one was fixed and the upper one movable.

The test film of a specific size was fixed between these two cell grips. The force was gradually applied until the film broke. The readings were recorded [13].

Folding Endurance: One film was repeatedly folded at the same place till it broke or folded up to a maximum number of times manually, which was considered satisfactory to reveal good film properties. Folding endurance is the number of times of film could be folded at the same place without breaking. This test was done on three films [14].

Percentage Moisture Absorption (PMA): The percentage moisture absorption test was carried out to check the physical stability of the oral films at high humid conditions.

Three films were cut out and weighed accurately, and then the films were placed in a desiccator containing a saturated solution of sodium chloride, keeping the humidity inside the desiccator at 75 %. After 3 days, the films were removed, weighed, and the percentage moisture absorption was calculated [19]. The average percentage moisture absorption of three films was found.

Percentage moisture absorption = (Final weight – Initial weight) / Initial weight × 100

Percentage Moisture Loss (PML): Percentage moisture loss was also carried to check the integrity of films in dry conditions. Three films were cut out and weighed accurately, and kept in a desiccator containing fused anhydrous calcium chloride. After 72 h the films were removed and weighed [19].

The average percentage moisture loss of three films was found out.

Percentage moisture loss = (Initial weight – Final weight) / Initial weight × 100

Disintegration Time: Disintegration time was calculated by taking 2.5 X 2.5 cm^2 sizes of films in the petri dish and soaking in 5 ml of PBS pH 6.8. Time taken by the film to disintegrate completely was noted. All the readings were done in triplicate and an average value was reported.

Drug Release: The *in-vitro* drug release of the films was carried out in a beaker with 50 ml phosphate buffer (pH 6.8) with 1 % w/v SLS at 37 $\pm$ 0.5°C. The assembly was placed on the shaker. An aliquot sample of 2 ml was taken at a different time interval, and the same amount was replaced with the media.

Drug Content Uniformity: Drug content uniformity was calculated by taking 2.5 X 2.5 cm^2 sizes of films in phosphate buffer. The solutions were filtered, and absorbance was measured in UV-spectrophotometer at nm using blank film solutions prepared similarly as above and used as a reference sample [18].

RESULTS AND DISCUSSION: The FTIR studies showed the possible interaction between drug excipients, which can be assured through the peaks obtained in IR spectra. As the peaks were retained in the mixture of the drug and excipient and no extra peak was formed, it could be concluded that no possible interaction has taken place. Formulation SD3 was found to be the most promising as our specifications, so it was taken up for further study. Rest batches are not shown in this paper.

TABLE 2: PREFORMULATION STUDY OF THE ACCEPTABLE BATCH

Code	Solvent (ml)	Drug (mg)	PEG 6000 (mg)	PF 127 (% w/w)	% Yield	Melting point (°C)	Observations
SD3	20	40	80	3	62.12	55	A

A: acceptable

TABLE 3: SOLUBILITY PROFILE AND DISSOLUTION STUDIES OF ACCEPTABLE BATCHES

S. no.	Formulations	Solubility (mg/ml) mean ± SD	Times fold increase in solubility	Q_{50}± SEM
1.	Quercetin	0.01 ± 0.003	-	14.30 ± 1.01
2.	PM1	0.012 ± 0.002	1.2	29.50 ± 1.01
3.	PM2	0.013 ± 0.001	1.3	21.39 ± 1.76
4.	PM3	0.015 ± 0.002	1.5	26.46 ± 1.01
5.	SD3	0.042 ± 0.005	4.2	36.59 ± 1.76

TABLE 4: DRUG CONTENT AND % YIELD OF FINALIZED FORMULATION

Formulations	% Drug content mean± SD	% Yield± SEM	Q_{50}± SEM
SD3	96.96 ± 0.27	60.12 ± 0.74	36.59 ± 1.76

Q50 = % of drug released in 50 min.

Scanning Electron Microscopy (SEM): The upper and lower sides of the obtained films were gold-sputtered for 180 s. Afterward, the distribution of quercitin solid dispersion and differences between the upper and lower side of the films was examined by scanning electron microscopy at a working voltage of 20 kV.

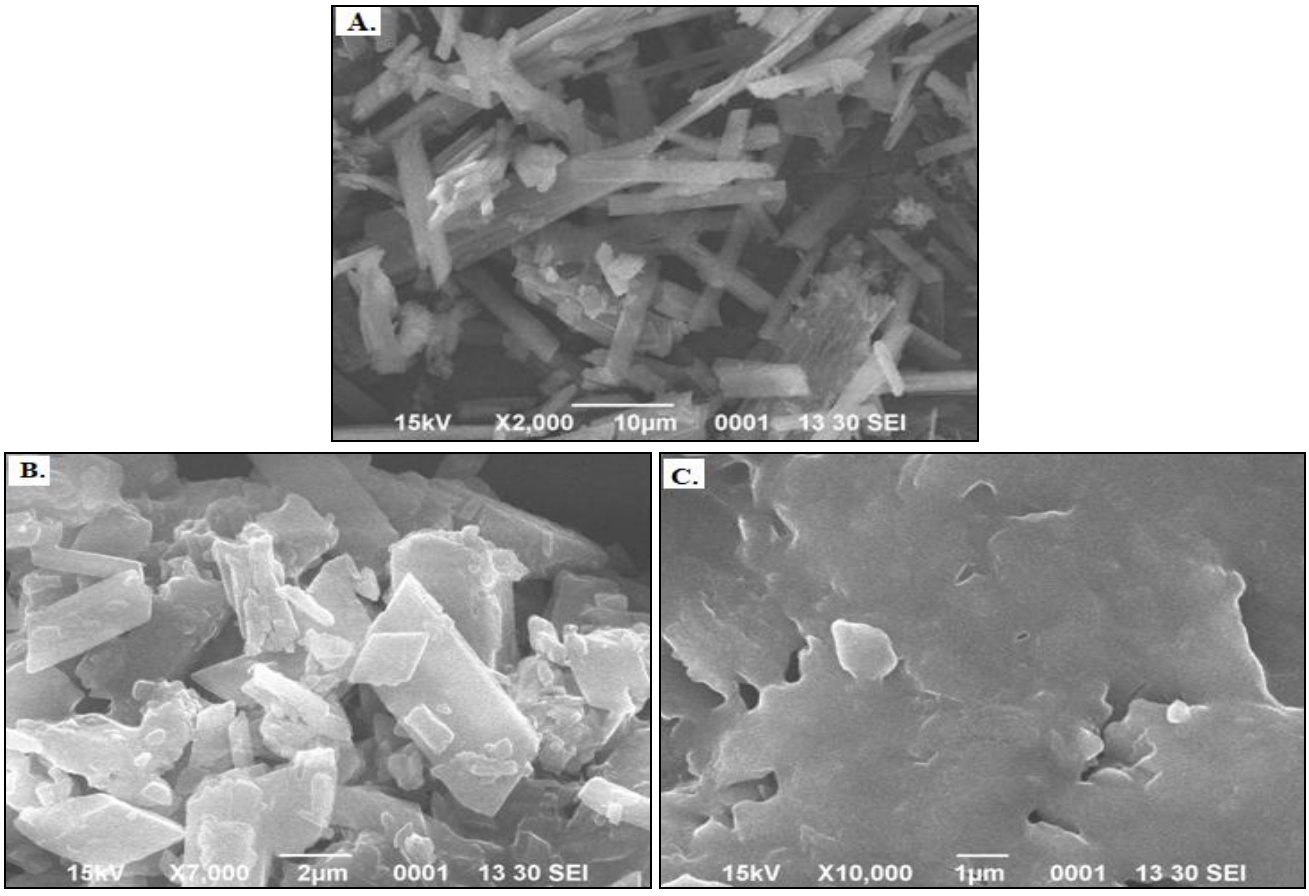

FIG. 1: SEM IMAGES OF A. PURE QUERCETIN, B. PHYSICAL MIXTURE AND C. SOLID DISPERSION

Morphological Studies: SEM images were taken to visualize the surface morphology of the wafers **Fig. 2.** PVA film showed minimal thickness while HPMC (15cps) film showed maximum thickness the optimal thickness of the film was obtained from HPMC (5cps) film. Propylene glycol showed minimal tensile strength while PEG 400 showed PEG200 showed optimal strength. Effect HPMC (5cps) showed minimal tensile strength while PVA showed maximal tensile strength where HPMC (15cps) optimum tensile strength. Propylene glycol showed minimal percentage elongation while PEG400 showed PEG200 showed optimal percentage elongation. Effect HPMC (5cps) showed minimal elongation, while PVA showed maximal percentage elongation where HPMC (15cps) optimum percentage elongation.

Best folding endurance was obtained by films that were made from the PVA polymer were as the least folding endurance was observed in the HPMC (5cps) films whereas HPMC (15cps) films showed optimal folding endurance. The propylene glycol polymer saw the maximum folding endurance was as the least folding endurance was observed in PEG400 films, whereas PEG200 films showed optimal folding endurance. PVA films showed minimum moisture absorption, whereas HPMC (5cps) showed maximum moisture absorption whereas HPMC (15cps) showed optimal moisture absorption. In the case of percentage moisture loss PVA films showed minimum moisture loss whereas HPMC (5cps) showed maximum moisture loss whereas HPMC (15cps) showed optimal moisture loss. Batch F3 showed the best release profile as it showed complete drug release in 120 sec. HPMC (5cps) film showed the least weight, whereas PVA films showed maximum weight; the weight of the HPMC (15cps) film showed optimum weight.

The pH of films varied from pH 7.4 to 7.9 as the drug incorporated is basic.

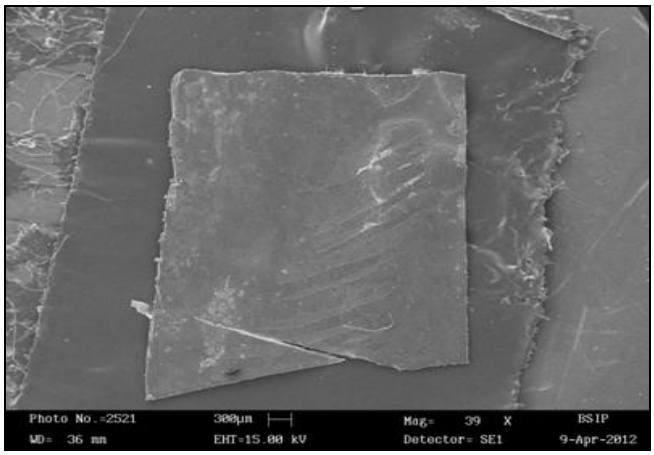

FIG. 2: SEM IMAGE OF FILM CONTAINING DRUG (BATCH F3)

Kinetics of Drug Release: The drug content uniformity of all the films was satisfactory and showed no significant variation. Kinetic assessment of drug release is shown in **Tables 5** & **6**.

TABLE 5: KINETIC DRUG STUDY OF FINALIZED FORMULATION

S. no.	Kinetic parameters	BATCHES					
		F1		F2		F3	
		R	K	R	K	R	K
1	Zero order	0.9286	0.0521	0.9684	0.0439	0.9110	0.0539
2	T-test	5.005	(Passes)	7.760	(Passes)	4.419	(Passes)
3	1st order	0.9287	-0.0005	0.9684	-0.0004	0.9111	-0.0005
4	T-test	5.008	(Passes)	7.766	(Passes)	4.421	(Passes)
5	Matrix	0.9918	0.0716	0.9872	0.0597	0.9953	0.0743
6	T-test	15.494	(Passes)	12.399	(Passes)	20.513	(Passes)
7	Peppas	0.9804	0.0673	0.9935	0.0532	0.9870	0.0723
8	T-test	9.963	(Passes)	17.518	(Passes)	12.274	(Passes)
9	Hix.Crow.	0.9286	-0.0002	0.9684	-0.0001	0.9111	-0.0002
10	T-test	5.007	(Passes)	7.764	(Passes)	4.420	(Passes)
11	t-Table at P0.05 (Two Tails), DF=n-2:-	2.776		2.776		2.776	
12	Best fit model-	Matri		Peppa		Matrix	

TABLE 6: KINETIC DRUG STUDY OF FINALIZED FORMULATION

S. no.	Kinetic parameters	Batches					
		F7		F8		F9	
		R	K	R	K	R	K
1	Zero order	0.9815	0.0407	0.9681	0.0360	0.9810	0.0412
2	T-test	10.244	(Passes)	7.731	(Passes)	10.117	(Passes)
3	1st order	0.9815	-0.0004	0.9682	-0.0004	0.9810	-0.0004
4	T-test	10.253	(Passes)	7.737	(Passes)	10.126	(Passes)
5	Matrix	0.9767	0.0551	0.9897	0.0490	0.9744	0.0556
6	T-test	9.092	(Passes)	13.854	(Passes)	8.675	(Passes)
7	Peppas	0.9803	0.0494	0.9943	0.0457	0.9759	0.0496
8	T-test	9.935	(Passes)	18.588	(Passes)	8.944	(Passes)
9	Hix.Crow.	0.9815	-0.0001	0.9682	-0.0001	0.9810	-0.0001
10	T-test	10.250	(Passes)	7.735	(Passes)	10.123	(Passes)
11	t-Table at P0.05 (Two Tails), DF=n-2	2.776		2.776		2.776	

DISCUSSION: Quercetin was found to be a yellow powder with a characteristic odor and crystalline nature. PEG 6000 was observed as white flakes and PF 127 showed off a white granular appearance. On a similar side, the physical mixture was a yellow granular powder and solid dispersions were observed as bright yellow irregular particles. The observations were under the findings reported in the kinds of literature. The melting point of quercetin was determined by melting point apparatus by capillary method and found to be in the range of 316-318℃, which is near to 316℃ reported in the literature.

The melting point of PEG 6000 ranged from 55 - 60℃ determined by the capillary method. Similarly, the capillary method found it in the range of 50 - 60℃, 55 - 65℃, 45 - 50℃ by the capillary method. The obtained drug can be identified as quercetin and the formation of the desired product can be indicated from the readings. Among all the batches prepared SD3 showed the highest drug content. Pure quercetin showed aqueous solubility of 0.01 ± 0.003mg/ml at 37℃, following the literature [21].

SD3 exhibited a maximum 4.2-fold increment in solubility as compared to unprocessed quercetin. Particle size reduction and an increase in the surface area lead to an increase in apparent solubility and solubilization effect. *In-vitro* dissolution studies were done for pure quercitin physical mixtures and prepared solid dispersion formulations. The images obtained through scanning electron microscopy (SEM) for quercetin (QC), physical mixture, and solid dispersion system showed morphological habit evaluation. In the SEM photomicrographs, pure quercetin displayed a non-uniform particle size that was needle-shaped. This is in line with the findings previously reported [22-24].

CONCLUSION: The potential of quercetin as a significant therapeutic agent has prompted increased interest in its diverse capacities as an antioxidant, anti-viral, anti-platelet, anti-inflammatory, antineoplastic, and cardio-protective agent. However, these potential activities cannot be utilized extensively due to their poor solubility. We formulated solid dispersions of quercetin by a solvent evaporation method to eradicate this issue. We found that solubility, as well as dissolution of quercetin, was significantly enhanced by solid dispersions formation. Release from pure quercetin was very low due to its low solubility. In contrast, the release from solid dispersions of quercetin was much faster. It can be concluded that the best film-forming polymer for fast dissolving oral film is HPMC (5cps) whereas the best plasticizer is propylene glycol. It can be said that based on the results obtained, the film HPMC (5cps) film showed minimal dissolution time with the best content uniformity and stability studies.

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