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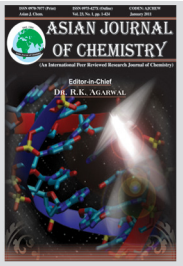

# Formulation and *in vitro* Evaluation of Quercetin-Cyclodextrin Tablets

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Quercetin is a natural bioflavonoid and it exhibits antiinflammatory, antioxidant and antitumor activities. However, because of its poor solubility and low oral bioavailability, the development of an orally bioavailable flavonoid-carrier system is of great importance clinically. Consequently, the rationale of this study quercetin by preparing its formulations with enhanced dissolution rate. Inclusion complexes of quercetin with cyclodextrins like β-cyclodextrins (βCD), hydroxyl propyl β-cyclodextrins (HP-βCD) and sulfa butyl β-cyclodextrins (SBE-βCD) were prepared by physical mixing and kneading method. Quercetin-CD (1:2) tablets were prepared by direct compression method. QT-βCD tablets exhibited higher dissolution rate than QT/QT-HP-βCD/QT-SBE βCD.

**Key Words: Quercetin, Cyclodextrins, Formulations.**

## INTRODUCTION

Flavonoids are present in most edible fruits and vegetables, but the type of flavonoids obtained from different dietary sources varies. Intake estimates for flavonoids are available for a few flavonoid subclasses such as flavonols, flavanones and isoflavones. The most common flavonol in the diet is quercetin. It is present in various fruits and vegetables, but the highest concentrations are found in onion[1]. The importance of different foods as quercetin sources varies between countries. Quercetin an aglycone, has been reported to exert numerous pharmacological activities such as antiinflammatory[2], antioxidant[3], anticarcinogenic effects[4] and are ingredients of numerous multivitamin preparations and herbal remedies. The poor aqueous solubility of the drug gives rise to difficulties in the formulation of solid dosage forms and varies the dissolution rate and bioavailability.

Pharmaceutical literature survey reveals that the application of cyclodextrins in enhancing the effectiveness of different formulations[5-7]. This efficiency of cyclodextrins is mainly attributed to their capacity (i) to enhance the solubility and dissolution of the drug, (ii) to enhance the bioavailability of the drug, (iii) to enhance the safety of the drug by reducing its irritation, (iv) to enhance the stability of the drug by reducing its vulnerability to dehydration, hydrolysis, oxidation and photo decomposition and (v) to enhance the permeability of the drug.

The solubility and dissolution rate of quercetin is very poor. From the earlier research paper[8], it was found that *in vitro* performance of CD complexes of quercetin is much better than that of pure drugs with respect to solubility dissolution rate. In the present work quercetin-CD kneaded complexes and physical mixtures at 1:2 molar ratios were selected for formulation studies.

Quercetin was a gift sample from AIE chemicals (USA), βCD and HP-βCD were gift samples from SA chemicals, Mumbai. SBE-βCD was purchased from Rouqette chemicals. Microcrystalline cellulose (Avicel 102) and pregelatinised starch were gift samples from Dr. Reddy's Laboratories, Hyderabad, Magnesium stearate and Talc were purchased from SD Fine Chem Ltd., Mumbai.

The physical mixtures of quercetin and CDs in 1:2 M were prepared by mixing pulverized powders and then passed through sieve of 100 mesh.

Inclusion complexes of quercetin in CDs under investigation were prepared by the kneading method[9] where by quercetin was added to cyclodextrin in a molar ratio to its corresponding stoichiometric ratio in the complex, kneaded thoroughly with 3 parts water and 2 parts methanol to obtain a paste which was then dried and the dried mass was pulverized and sieved through a 100 mesh sieve.

Compressed tablets each equivalent to 20 mg of quercetin were prepared by direct compression method employing quercetin and different CDs like βCD, HP-βCD and SBE-βCD in 1:2 Kn and 1:2 Pm and using microcrystalline cellulose (Avicel 102) as directly compressible vehicle, pregelatinised starch, magnesium stearate (1 %) and talc (1 %) were also

TABLE-1
FORMULAE OF QUERCETIN, QUERCETIN-CD 1:2 Kn AND 1:2 Pm BINARY SYSTEMS

| Ingredient (mg/tab.) | Formulation | | | | | | |
|---|---|---|---|---|---|---|---|
| | QF1 | QF2 | QF3 | QF4 | QF5 | QF6 | QF7 |
| QT | 20 | – | – | – | – | – | – |
| QT-βCD1:2 Kn | – | 171 | – | – | – | – | – |
| QT-βCD1:2 Pm | – | – | 171 | – | – | – | – |
| QT-HP-βCD1:2 Kn | – | – | – | 207 | – | – | – |
| QT-HP-βCD1:2 Pm | – | – | – | – | 207 | – | – |
| QT-SBE-βCD1:2 Kn | – | – | – | – | – | 327 | – |
| QT-SBE-βCD1:2Pm | – | – | – | – | – | – | 327 |
| MCC | 168 | 171 | 171 | 207 | 207 | 327 | 327 |
| Pregelatinious starch | 8 | 14 | 14 | 18 | 18 | 26 | 26 |
| Magnesium stearate + talc | 2+2 | 4+4 | 4+4 | 5+5 | 5+5 | 7+7 | 7+7 |
| Total weight of tablet (mg) | 200 | 364 | 364 | 442 | 442 | 694 | 694 |

TABLE-2
DRUG CONTENT, HARDNESS, FRIABILITY AND DISINTEGRATION TIME AND DISSOLUTION PARAMETERS OF QUERCETIN-CD 1:2 Kn AND 1:2 Pm BINARY SYSTEMS TABLETS

| Tablet formulation | Quercetin content (mg/tab) | Hardness ($kg/cm^2$) | Friability (%) | Disintegration time (min) | $K_1$ ($min^{-1}$) | $T_{50}$ (min.) | $DE_{10}$ (%) | Per cent drug dissolved in 10 min |
|---|---|---|---|---|---|---|---|---|
| QF1 | 98.2 | 5.0 | 0.50 | 1.0 | 0.0063 | 109 | 11.6 | 18.9 ± 0.36 |
| QF2 | 99.1 | 5.2 | 0.82 | 4.0 | 0.135 | 5.1 | 51.8 | 73.1 ± 0.60 |
| QF3 | 98.5 | 5.5 | 0.80 | 5.0 | 0.102 | 7 | 30.5 | 47.2 ± 0.40 |
| QF4 | 98.3 | 6.0 | 0.68 | 16.0 | 0.070 | 10 | 28.8 | 44.5 ± 0.61 |
| QF5 | 99.0 | 6.2 | 0.68 | 17.0 | 0.057 | 12 | 26.0 | 41.4 ± 0.85 |
| QF6 | 98.0 | 6.4 | 0.96 | 24.0 | 0.055 | 13 | 23.5 | 36.4 ± 0.62 |
| QF7 | 98.5 | 6.5 | 0.95 | 23.0 | 0.027 | 25 | 19.6 | 31.0 ± 0.89 |

incorporated as per the formulae given in Table-1. All the ingredients were blended thoroughly in a closed high density polyethylene bottle and were directly compressed into tablets to a hardness of 5-6 $kg/cm^2$ on a 16-station Cadmach tablet machine. The tablets were prepared and evaluated for hardness, friability and disintegration of the tablet was assessed. Quercetin content estimated by a reported UV spectrophotometric method.

The dissolution rate of quercetin from the tablets was studied in 900 mL of water containing 0.75 % SLS using REMI USP dissolution test apparatus with paddle stirrer at 50 rpm. A temperature of 37 ± 1 ºC was maintained throughout the study. One tablet equivalent to 20 mg of quercetin-CD was used in each test. Samples of dissolution media (5 mL) were withdrawn and filtered through a filter (0.45 mm) at time interval 5, 10, 20, 30, 45, 60, 75, 90 and 120 min, suitably diluted and assayed for quercetin at 370 nm, respectively. The sample of dissolution fluid withdrawn at each time was replaced with fresh dissolution fluid. The dissolution experiments were conducted in triplicate.

## RESULTS AND DISCUSSION

The hardness of tablets produced by formulae of quercetin and its binary mixtures varied from 5.0-6.5 $kg/cm^2$. The friability values of all the batches of tablets, both of quercetin and its binary systems were found to be less than 1 %. Drug content uniformity is seen among all the tablets of a batch prepared by these different formulae. All the formulations satisfied the content of the drug as they contained with in 100 ± 2 % of the label claim.

For quercetin all the batches of tablets dissolution rate followed by first order kinetics. Quercetin-βCD (1:2) tablets (QF2 and QF3) exhibited the highest dissolution rate than quercetin (QF1). A 4.87 fold increase in the dissolution rate of quercetin was observed with these tablets when compared to plain quercetin-βCD tablets. Dissolution efficiency (DE10) values were calculated as suggested by Khan[10]. Quercetin-CD tablets of disintegration time, K ($min^{-1}$) values, $T_{50}$ (min) and ($DE_{10}$), values are shown in Table-2.

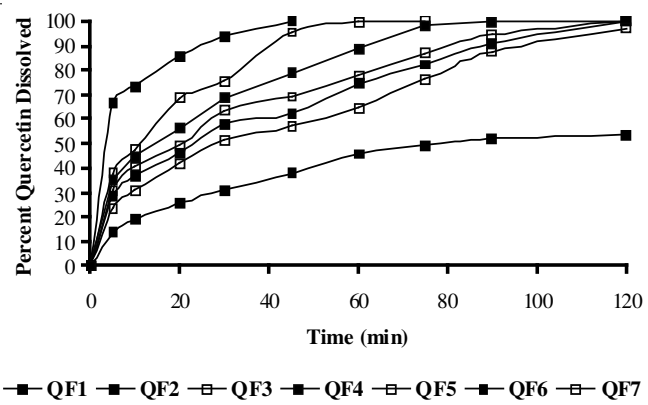


Fig. 1. Dissolution profiles of quercetin, quercetin-CD 1:2 Kn and 1:2 Pm formulations

Dissolution efficiency and *in vitro* dissolution rate is in the order of quercetin-βCD > quercetin-HP-βCD > quercetin-SBE-βCD tablets. These results also indicate that in all cases, in quercetin tablets with complexes produced by kneading method give better dissolution efficiency than tablets with complexes produced by physical mixing. Thus, quercetin tablets with very rapid disintegration and dissolution rate could be produced by employing their complexes with βCD.

Quercetin-CD inclusion complexes of dissolution enhancement were reverse when tablets of the quercetin-CD inclusion complexes were tested. Chowdary and Sambasivarao[11] also reported a similar finding in their work involving aceclofenac-CD tablets. Quercetin-CD tablets formulated by direct compression method were of good quality with regard to hardness, friability and drug content. Quercetin-βCD tablets exhibited significantly higher dissolution rate and efficiency than plain, quercetin-HP-βCD and quercetin -SBE-βCD tablets. The poor disintegration and dissolution characteristics observed with and quercetin-HP-βCD/SBE-βCD tablets are due to dry binding nature and swelling factor of HP-βCD and SBE-βCD. Particularly SBE-βCD and HP-βCD were suitable in parenteral and liquid formulation.

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