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RESEARCH PAPER

Fast- and Slow-Release Tablets for Oral Administration of Flavonoids: Rutin and Quercetin

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ABSTRACT

Many derivatives of rutin (Rt) and its metabolite quercetin (Q) are employed in clinics for cardiovascular chronic pathology, and are also known for their anti-ulcer behavior in vivo and antiproliferative and antimutagenic activity in vitro. Unfortunately, the absorption of quercetin and rutin from the gastrointestinal tract is slow and irregular, probably due to their very slight solubility in water and slow dissolution rate.

In this work the dissolution rate of the drugs from oral formulations has been improved using some enhancers such as cross-linked sodium carboxymethylcellulose (CMC-XL), sodium carboxymethylstarch (E), and cross-linked polyvinylpyrrolidone (P). The drugs were loaded on the hydrophilic carriers by different techniques such as mixing or co-milling. The in vitro dissolution profiles of the mixed or co-milled drug/polymer systems, obtained in various media with different pH, were compared. The results show that the drug dissolution rate from the co-milled drug/carrier systems is faster than that from mixed systems, and CMC-XL and sodium carboxymethylstarch systems are able to enhance the dissolution rate. For this reason, these co-milled drug/carrier systems were used for the production of both fast- and slow-release tablets. The co-milled drug/CMC-XL

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system was used for the preparation of fast-release tablets containing rutin, while three different fast-release tablets were formulated and tested using respectively Q/CMC-XL, Q/E, and Q/P co-milled systems.

The effect of the presence of sodium lauryl sulfate in the aqueous medium on the dissolution profile of flavonoids alone was also studied.

The prolonged-release formulations have been developed using hydroxypropylmethylcellulose (HPMC) of different viscosity grades as retarding polymer. An extended release of the drugs for times ranging from 6 to 14 hr could be obtained, depending on the type and viscosity of the HPMC used.

Key Words: *Cross-linked polymers; Dissolution rate enhancer; Fast-release formulations; Flavonoids; Hydroxypropylmethylcellulose; Quercetin; Rutin; Surfactant; Sustained-release formulations*

INTRODUCTION

Flavonoids are naturally-occurring substances possessing some positive effects on human health and present in more than 100 preparations marketed in Europe (1). Many reviews have dealt with their structure, properties, and biosynthesis. These molecules show various biological effects, such as capillarity fragility protection (2), inhibition of lipid peroxidation (3), and anti-inflammatory activity through inhibition of the enzymes involved in arachidonate metabolism (4,5). In particular, rutin (Rt) and its metabolite quercetin (Q) (Fig. 1) are flavonoids widely distributed in herbal drugs. In recent years many rutin derivatives have been employed in clinics to treat cardiovascular chronic pathology such as venous insufficiency, hemorrhoids, and limphoedema (3); quercetin has shown antiulcer behavior in vivo (6), and antiproliferative and antimutagenic activity in vitro (7).

Unfortunately, these flavonoids are slightly soluble in water and show a slow dissolution rate from solid oral forms, restricting their use in therapy. It

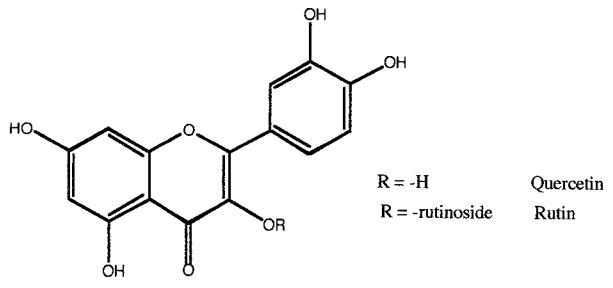

Figure 1. Structure of rutin (Rt) and its aglycon quercetin (Q).

is well known that the drug dissolution rate can be the critical limiting step in the bioavailability after oral administration and the therapeutic effect of the drug. In the case of low-solubility drugs, the drug absorption from the gastrointestinal tract is generally slow and irregular (8), and any enhancement of the dissolution would improve its absorption and bioavailability. For this reason, in the first step of this work, we tried to improve the dissolution rate of Rt and Q by loading onto the polymeric surface of some superdisintegrants, such as cross-linked sodium carboxymethylcellulose (CMC-XL), sodium carboxymethylstarch (E), and cross-linked polyvinylpyrrolidone (P). Mixing and co-milling were tested as loading techniques. These polymers, which are highly hydrophilic but insoluble in water, are able to absorb a large amount of water and swell to a great extent. In this way, the interaction with water of the drug particles present on the surface of the polymers is highly promoted, and their wetting properties are increased. As a result the dissolution rate of the drugs can be improved (9,10).

Since the use of surfactant solutions as dissolution media has been reported to enhance the dissolution rate of drugs characterized by low water-solubility, the effect of an aqueous solution of sodium lauryl sulfate (SLS) on the dissolution profiles of rutin and quercetin was also studied (11). Generally, aqueous solutions of such surfactants may simulate the physiological environment. Moreover, some studies showed that the presence of natural surfactants, such as bile salts, in the dissolution medium gives results comparable to those obtained using synthetic and less-expensive molecules such as SLS (12).

In the second step of this work either fast-release tablets or slow-release tablets were produced.

The design and development of a sustained-release formulation, containing a drug of very low solubility, are particularly difficult. It should be a compromise between the enhancement of the dissolution rate of the drug and the modulation of the delivery rate from the dosage form. To obtain an extended and slow release of the drugs, hydrophilic swellable matrices were formulated using hydroxypropylmethylcellulose (HMPC) of different viscosity grades, which is reported to determine a controlled release of drugs (13,14).

The dissolution properties of pure flavonoids, rutin and quercetin, flavonoid/carrier systems, and fast- and slow-release tablets are evaluated and compared.

MATERIALS AND METHODS

Materials

Rutin (Rt) and quercetin (Q) were supplied by Sigma-Aldrich Chemie GmbH P.O., Steinheim, Germany. Cross-linked sodium carboxymethylcellulose (CMC-XL) (Acdisol®, FMC Corporation, Philadelphia, PA) and sodium starch glycolate (E) (Explotab®, Mendell, Patterson, NY) were used as dissolution rate enhancers.

Polyvinylpyrrolidone (PVP) (PVP K30) and cross-linked polyvinylpyrrolidone (P) (Polyplasdone® XL-10) were supplied by ISP Corporation, Wayne, NY.

Other excipients were: colloidal silicon dioxide (Syloid® 244, Grace GmbH, Worms, Germany), spray-dried lactose (Pharmatose® DCL 11, DMV International, Veghel, Netherlands), magnesium stearate, and sodium lauryl sulfate (SLS), all of USP grade, supplied by C. Erba, Milan, Italy; microcrystalline cellulose (Pharmacel® 102, DMV International, Veghel, Netherlands).

Hydroxypropylmethylcellulose (Methocel® K4M: viscosity 4000 cP; K15M: 15,000 cP; K100M: 100,000 cP; Methocel® E5: 5 cP; Methocel® E50: 50 cP, viscosity values stated by the supplier and measured at 20°C on 2% w/v aqueous solution, Ubbelohde apparatus) was supplied by Colorcon Limited, Orpington, UK.

Methods

The particle size analysis of the drugs (raw material) was carried out with a laser light-scattering granulometer (Beckman Counter LS 230, Particle Volume Module Plus, UK). The drugs were suspended in saturated water and the analysis was made in triplicate.

Table 1

Drug Solubility (mg/L) at Room Temperature

	Rutin	Quercetin
Distilled water	45	7.7
GF	26	5.4
IF	128	28.87

The solubility of the drugs was evaluated spectrophotometrically in water, simulated gastric fluid (GF), and simulated intestinal fluid (IF) at room temperature (25°C) (see Table 1). The drug concentrations were measured spectrophotometrically at 352 nm for Rt and at 366 nm for Q (Spectracomp 602, Advanced Products srl, Milan, Italy).

Calibration curves were prepared in distilled water, USP 24 GF and IF (pH 1.2 and 7.5, respectively), both without enzymes. The proportionality between absorbance and concentration was verified in the range from 5 to 20 mg/L at room temperature for both rutin and quercetin ($R^2 > 0.999$ for both drugs).

Preparation of Drug/Carrier Systems

The drug/polymer systems were produced using sodium carboxymethylcellulose (CMC-XL) for Rt (Rt/CMC-XL) and cross-linked sodium carboxymethylcellulose (Q/CMC-XL), sodium carboxymethylstarch (Q/E), and cross-linked polyvinylpyrrolidone (Q/P) for Q. Drug/carrier systems (each batch of about 30 g) were prepared by mixing (Rt/CMC-XL mix; Q/CMC-XL mix; Q/E mix; Q/P mix) or co-milling (Rt/CMC-XL mil; Q/CMC-XL mil; Q/E mil; Q/P mil) techniques. In all cases the drug and the polymer, in the ratio 1:5, were placed in a mixing jar and mixed in a Turbula apparatus (W.A. Bachofen, Basel, Switzerland) at a speed of 30 rpm for 2 hr, or co-milled in an automatic mill (Retsch, Type RM0, Germany) for 15 min.

Preparation of Fast-Release Tablets

For Rt, fast-release tablets were formulated using Rt/CMC-XL mixed or Rt/CMC-XL co-milled systems, while for Q drug/co-milled systems were used. The compositions of the tablets are reported in Table 2. The fast-release tablet formulations were

Table 2

Fast-Release Tablets: Composition (mg)

	Rt1	Rt2	Rt3	QC1	QE1	QP1
Rt/CMC-XL mix[a]	120	120	—	—	—	—
Rt/CMC-XL mill[b]	—	—	120	—	—	—
Q/CMC-XL mill[b]	—	—	—	30	—	—
Q/P mill[b]	—	—	—	—	30	—
Q/E mill[b]	—	—	—	—	—	30
Sodium starch glycolate	50	50	50	50	50	50
Magnesium stearate	2	2	2	2	2	2
Sodium lauryl sulfate	—	2	2	2	2	2
Colloidal silicon dioxide	1	1	1	1	1	1
Total weight	173	175	175	85	85	85

[a]Mixed system with cross-linked carboxymethylcellulose (CMC-XL). Total drug content was 20 mg for rutin and 5 mg for quercetin.
[b]Co-milled systems with cross-linked carboxymethylcellulose (CMC-XL), cross-linked polyvinylpyrrolidone (P), or sodium starch glycolate (E) in a 1 : 5 ratio.

prepared as follows: the drug/polymer systems were mixed with or without SLS, with sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide in a Turbula Mixer (Bachofen, Basel, Switzerland) for 30 min. Then, the tablets Rt1, Rt2 (both containing Rt/CMC-XL mixed system), Rt3 (containing Rt/CMC-XL co-milled system), and QC1, QP1, QE1 (containing Q/CMC-XL co-milled system, Q/E co-milled system, and Q/P co-milled system, respectively) were obtained by direct compression using a single-punch machine (Korsch EK0, Berlin, Germany) equipped with plane punches 7 mm in diameter.

Preparation of Slow-Release Tablets

The formulation proposed for the sustained release of both drugs was designed as hydrophilic matrices containing HPMC with different viscosity grades as retarding polymer and cross-linked sodium carboxymethylcellulose as hydration enhancer. The compositions are reported in Table 3. The drug/CMC-XL systems were mixed with SLS and HPMC. For Q, microcrystalline cellulose was added as diluent. All the mixtures were wetted with a 10% (w/v) PVP ethanol solution. The wetted mass was forced through a 30 mesh screen (ATSM 600 μm). The granules were dried in a circulating air oven, to reach constant weight, and then calibrated through the same screen. Magnesium stearate and colloidal silicon dioxide were added to the granules and mixed in a Turbula Mixer (Bachofen, Basel, Switzerland) for 20 min.

The slow-release tablets were produced using the same machine and punches detailed above.

Table 3

Slow-Release Tablets: Composition (mg)

	Rutin	Quercetin
Rt/CMC-XL mill[a]	120	—
Q/CMC-XL mill[a]	—	30
Microcrystalline cellulose	—	75
Sodium lauryl sulfate	2	2
HPMC[b]	50	60
Polyvinylpyrrolidone	5	10
Magnesium stearate	2	2
Colloidal silicon dioxide	1	1
Total weight	180	180

[a]Drug co-milled with cross-linked carboxymethylcellulose (CMC-XL) in a 1:5 ratio. Total drug content was 20 mg for rutin and 5 mg for quercetin.
[b]Hydroxypropylmethylcellulose: Methocel E5, E50, K4, K15, K100.

Dissolution Studies

In vitro dissolution/release tests were carried out using the USP 24 dissolution test apparatus no. 2: paddle, 100 rpm at 37°C, in 1000 mL of IF and

1000 mL of distilled water. In addition, the dissolution tests of drug/carrier systems were carried out in 1000 mL of water containing 0.75% SLS and the tests on rutin slow-release tablets were carried out with a pH change method: 750 mL of HCl 0.1 N (pH 1) from 0 to 2 hr of the test, and then addition of 250 mL of 0.2 M tribasic sodium phosphate solution to give a final pH of 6.8, in a total volume of 1000 mL (USP 24 drug-release test, method A for enteric-coated particles). All the dissolution/release tests were made in triplicate; only the mean values are reported here (standard deviations < 5%).

In all cases the drug content was 5 mg of quercetin and 20 mg of rutin.

RESULTS AND DISCUSSION

The particle size analysis of Rt and Q shows that Rt has a mean volume diameter of 10 μm, Q of 26 μm, and they are micronized products.

The preliminary data on the solubility of these drugs show that Rt and Q have a pH-dependent solubility (Table 1). As reported for other flavonoids, the solubility of Rt and Q increases in the order GF > water > IF, due to salt formation of these weak acids in basic medium. As expected, the presence of the rhamnoglucoside moiety linked to the aglycon in the Rt molecule affords a solubility higher than the aglycon (Q) in all media (Fig. 1).

To improve the dissolution rate of Rt, the drug was loaded on CMC-XL, in the ratio 1 : 5, by mixing or co-milling. Since quercetin is less soluble than rutin, three different drug/carrier systems, in the ratio 1 : 5, were prepared and tested. In all systems tested the drug content was 5 mg for Q and 20 mg for Rt.

In Fig. 2 the dissolution profiles of Rt/CMC-XL mixed or co-milled systems and of drug alone in water and IF (pH 7.5) are reported. The faster dissolution profiles are shown by the drug/CMC-XL systems obtained by co-milling. After 5 min all the dose of rutin from the Rt/CMC-XL co-milled system was dissolved in water and IF, while about 32–38% of rutin from the Rt/CMC-XL mixed system and 7–13% of drug alone were dissolved in the same time. Thus the dissolution rate seems to be dependent on the technique used for loading the drug.

The efficiency of the different polymeric carriers used for quercetin was studied by comparing the dissolution profiles of mixed and co-milled

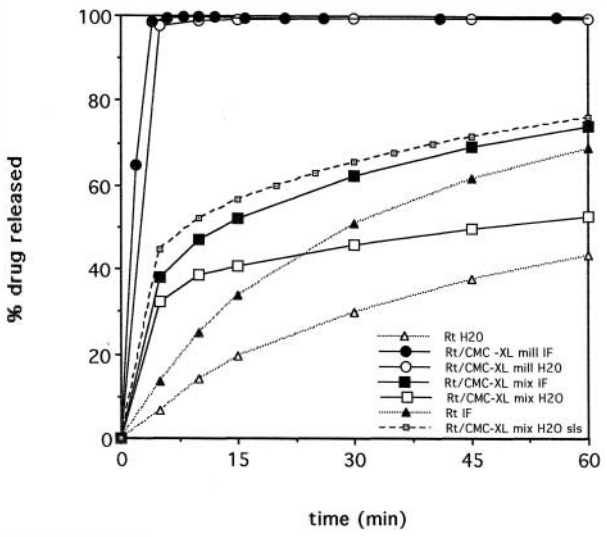

Figure 2. Dissolution profiles of Rt/CMC-XL mixed (Rt/CMC-XL mix) or co-milled (Rt/CMC-XL mill) systems and drug alone in water and IF (pH 7.5) compared to Rt/CMC-XL mixed system in 0.75% SLS solution (Rt/CMC-XL mix sls).

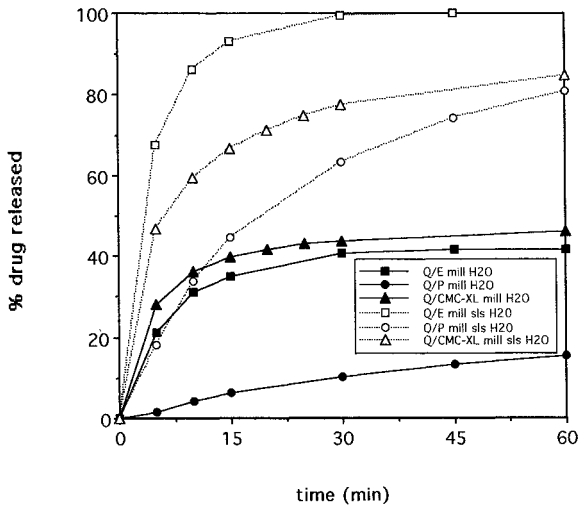

Figure 3. Dissolution profiles of Q/CMC-XL, Q/E, and Q/P co-milled systems in distilled water compared to same systems in 0.75% SLS aqueous solution.

Q/CMC-XL, Q/E, and Q/P with the drug alone in distilled water. Also in this case the dissolution profiles were dependent on the procedure; the co-milled systems Q/CMC-XL and Q/E show dissolution rates faster than the Q/P system and drug alone (Fig. 3)

and faster than the respective mixed systems (data not shown). The dissolution profiles in water show that about 35–42% of drug was released in 15 min from Q/CMC-XL or Q/E systems, while about 6% of drug was dissolved from the Q/P system or drug alone in the same time.

Moreover, an analysis of the dissolution profiles of the co-milled drug/carrier systems in water or 0.75% SLS solution showed that the dissolution rate of these drugs is enhanced in the presence of SLS. In fact, all the drug was released within 30 min from the Q/E co-milled system, about 77% from the Q/CMC-XL co-milled system, and about 63% from the Q/P co-milled system in 0.75% SLS solution. Meanwhile about 40–43% was released from the Q/E or Q/CMC-XL co-milled systems and about 10% from the Q/P co-milled system in the same time in water (Fig. 3). From the above data, the co-milled systems were selected for the production of fast- and slow-release tablets containing Q (see Tables 2 and 3).

For rutin, within 30 min only 45% of the drug was released from Rt/CMC-XL mixed system in water, while about 65% was released in 0.75% SLS aqueous solution in the same time (Fig. 2).

The fast-release formulation containing rutin was prepared with drug/CMC-XL co-milled (Rt3) or mixed (Rt2) systems, using sodium starch glycolate as superdisintegrant and SLS as surfactant (Table 2). The dissolution rate of Rt2 or Rt3 was compared to the fast-release tablets containing Rt/CMC-XL mixed system without SLS (Rt1) in distilled water. The release of the drug from Rt2 was faster than Rt1; this seems to be due to the presence of a surfactant such as SLS in Rt2 that improves the wettability and dissolution rate of the drug. Only from the formulation Rt3 was all the dose of rutin released in 60 min (Fig. 4), confirming that the co-milling technique gives a better dissolution rate of the drug.

The dissolution profiles of Rt2 and Rt3 in IF are superimposable on those in water (Fig. 4). In fact, within 15 min about 90% of Rt was released from Rt3, while about 70% of drug was released from Rt2 in the same time.

For quercetin, three fast-release formulations were prepared using co-milled Q/CMC-XL (QC1), Q/sodium starch glycolate (QE1), and Q/cross-linked polyvinylpyrrolidone (QP1) systems respectively, with SLS as surfactant to improve the wettability of the drug and sodium starch glycolate as superdisintegrant. The dissolution profiles in water

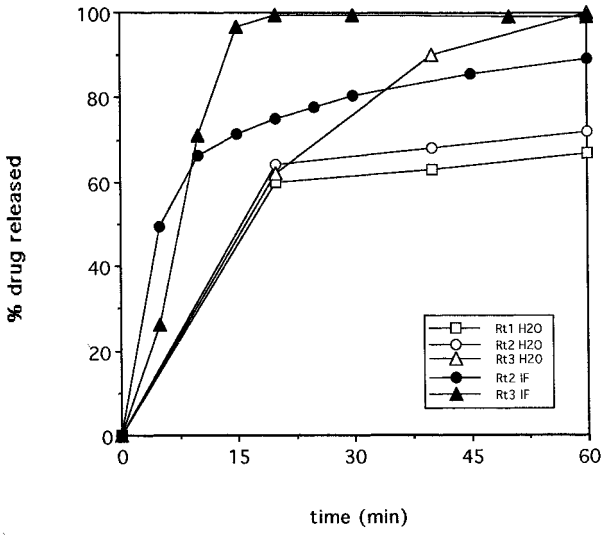

Figure 4. Dissolution profiles of fast-release tablets containing Rt in water and IF (pH 7.5): Rt1 contains Rt/CMC-XL mixed systems; Rt2 contains Rt/CMC-XL mixed system and SLS; Rt3 contains Rt/CMC-XL co-milled system and SLS.

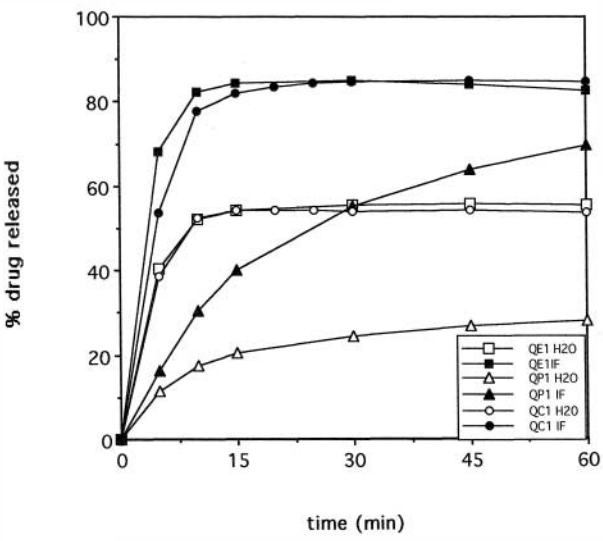

Figure 5. Dissolution profiles of fast-release tablets containing Q in IF (pH 7.5) and distilled water: QC1 contains Q/CMC-XL co-milled system; QP1 contains Q/P co-milled system; QE1 contains Q/E co-milled system.

and IF show that, as for the dissolution rates of the respective Q/carrier systems, QC1 was comparable with QE1 and both these formulations are faster in the release than QP1 (Fig. 5). In fact, within 5 min

about 68% of drug is released from QE1, and about 50–55% from QC1, while only about 16% from QP1 in IF. About 40% is released from QC1 and QE1 and only about 1% from QP1 in water. However, no more than 80–85% of Q in IF and 55% in water was released from these formulations.

Given the above results, the sustained-release tablets were formulated using both drug/CMC-XL co-milled system and SLS + HPMC as hydrophilic swellable retarding polymer (Table 3).

The release profiles of the hydrophilic matrices containing rutin in IF (Fig. 6) and with pH variation method (Fig. 7) show that the drug release rate is related to the different viscosity of HPMC used. In fact, the matrices RtE5 and RtE50 containing HPMC of lower viscosity (5 and 50 cP, respectively) dissolve more quickly (30 min) compared to matrices RtK4, RtK15, and RtK100, containing HPMC of higher viscosity. These observations are in good agreement with several previous papers which reported that HPMC of a higher viscosity is able to modulate the delivery rate of the drug (13).

Increasing the HPMC viscosity grade, the dissolution rate is reduced progressively. About 90% of the drug is released within 5 hr for HPMC K4 (RtK4), 6 hr for HPMC K15 (RtK15), and 10 hr for HPMC K100 (RtK100) in IF (Fig. 6), while with the pH variation method the same dose is released within 5 hr for HPMC K4 (RtK4), 8 hr for HPMC K15 (RtK15), and 12 hr for HPMC K100 (RtK100) (Fig. 7). An analysis of the dissolution profiles of hydrophilic matrices containing rutin showed considerable differences in IF and with the pH change method only in the case of formulations containing HPMC of high molecular weight. In fact, slower dissolution rates can be detected with the pH change method in particular from RtK15 and RtK100 matrices. A sudden increase in the drug release rate (flex point) after a certain time can be explained by the prevalence of matrix erosion over the swelling process (Fig. 7).

Since we have obtained only an incomplete release of Q, about 45–50% from drug/carrier systems and 80–85% from fast-release tablets in IF, slow-release tablets were formulated using microcrystalline cellulose as diluent. This excipient was used to increase the tablet weight of slow-release tablets and to promote the water absorption, because it has a slight disintegrant effect. The presence of this diluent seems able to deliver all the Q content, but in such formulations the presence

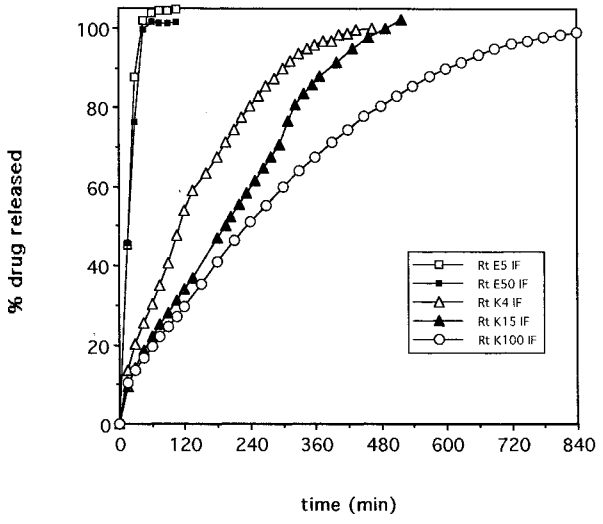

Figure 6. Rutin: dissolution profiles of prolonged-release hydrophilic matrices containing HPMC of different viscosity in IF (pH 7.5). RtE5: tablets with HPMC 5 cP; RtE50: tablets with HPMC 50 cP; RtK4: tablets with HPMC 4000 cP; RtK15M: tablets with HPMC 15,000 cP; RtK100M: tablets with HPMC 100,000 cP.

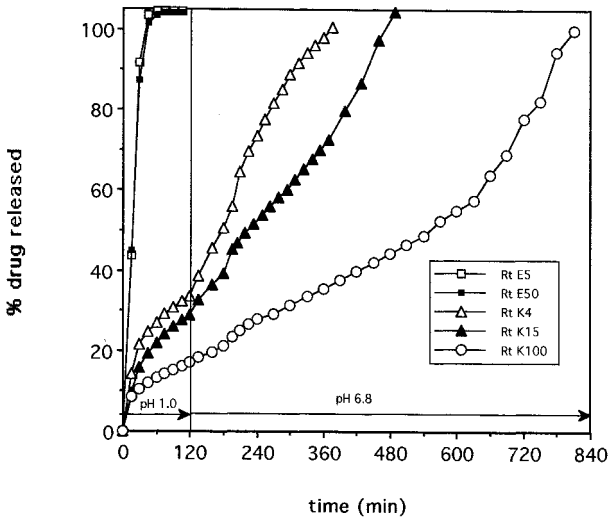

Figure 7. Rutin: dissolution profiles of prolonged-release hydrophilic matrices containing HPMC of different viscosity with pH change method: pH 1.0 from 0 to 2 hr; pH 6.8 from 2 hr on (see Methods). RtE5: tablets with HPMC 5 cP; RtE50: tablets with HPMC 50 cP; RtK4: tablets with HPMC 4000 cP; RtK15M: tablets with HPMC 15,000 cP; RtK100 M: tablets with HPMC 100,000 cP.

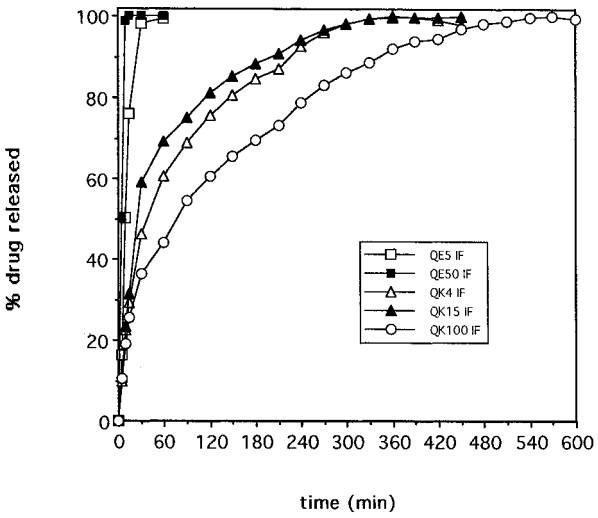

Figure 8. Quercetin: dissolution profiles of prolonged-release hydrophilic matrices containing HPMC of different viscosity in IF (pH 7.5). QE5: tablets with HPMC 5 cP; QE50: tablets with HPMC 50 cP; QK4: tablets with HPMC 4000 cP; QK15 M: tablets with HPMC 15,000 cP; QK100 M: tablets with HPMC 100,000 cP.

of the retarding polymer seems less efficient in controlling the release rate and a burst effect is always evident (Fig. 8).

CONCLUSIONS

Rutin and quercetin are flavonoids with low solubility in biological fluids, but Rt is more soluble than Q due to the presence of a saccharidic moiety in the molecule.

The co-milling of these drugs with a dissolution enhancer, either cross-linked sodium carboxymethylcellulose or sodium starch glycolate, produces a slight enhancement of the dissolution rate, and the co-milling technique has proved more efficient compared to the mixing technique.

In the fast-release tablets, the presence of a superdisintegrant, such as sodium starch glycolate, and a surfactant, such as sodium lauryl sulfate, improved the dissolution rates of both drugs.

In the formulation of extended-release matrices, HPMC of low molecular weight is not effective in prolonging the drug-release process, while HPMC of higher molecular weight seems able to modulate the dissolution rate of the drugs.

However, the rate of dissolution of the less soluble drug Q is also affected by the presence of other excipients, such as microcrystalline cellulose, which shows a disintegrant effect too. The results of the present study suggest that these materials play an important role in the erosion process of the matrices.

In conclusion, the hydrophilic matrices containing HPMC of higher viscosity were able to modulate the delivery of drug from the oral dosage form. In fact, all the drug content was released over times ranging from 5 to 8 hr for Q and 6 to 14 hr for Rt.

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