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# Sustained release from matrix system comprising hydrophobic and hydrophilic (gel-forming) parts

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## Summary

A study has been made of the in vitro release from a matrix comprising hydrophobic and hydrophilic (gel-forming) components containing three non-steroidal antiinflammatory agents with differing solubility and wettability (indomethacin, ibuprofen and diclofenac sodium). Tensile strength and drug release rate were studied as functions of drug content, compression pressure and stirring during dissolution testing. Both were dependent on the wettability of the drug. Release rate decreased with drug/matrix ratio for wettable, soluble diclofenac but increased with indomethacin and ibuprofen. The release rate changes are explained on the basis of the interaction between the gel and other matrix components in the presence of water.

## Introduction

Hydrogenated vegetable oil and carboxypolymethylene (Carbopol), have been used separately in the production of sustained release systems as insoluble (skeleton) and erodible matrices for oral administration (Ritschel, 1973; Johnson, 1974). Diffusion and erosion mechanisms have been combined recently using hydrogel systems offering advantages in release profile (Colombo et al., 1987; Shah et al., 1989) and it was considered appropriate to examine how diffusion and erosion combine in a matrix comprising an insoluble hydrophobic and a hydrophilic gel-forming element using hydrogenated vegetable oil and carboxypolymethylene, respectively. By employing conventional wet granulation and tableting, the principle was tested using three non-steroidal anti-inflammatory agents with differing solubility, wettability and dose size. The aim is to establish any correlation between solubility or wettability of the added active ingredients and release from matrices with different drug content. Such a correlation might provide information about the design of a general erosion-diffusion oral sustained release matrix system.

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## Experimental

*Materials and methods*

The nonsteroidal anti-inflammatory drugs were: indomethacin (Geopharma, Milan, Italy), ibuprofen (Boots Co., Nottingham, U.K.) and diclofenac sodium (Heumann Pharma GmbH, Nürnberg, Germany). Hydrogenated vegetable oil NF XVI (Emvelop, m.p. 61–66 °C, Forum, Surrey, U.K.) and carboxypolymethylene (Carbopol 934, Honeywill and Stein Ltd, London, U.K.) were the main matrix forming materials. Microcrystalline cellulose (Avicel pH 101, FMC, Little Island, Ireland) was selected as wicking agent and isopropanol (Fisons, Loughborough, U.K.) as granulating liquid. Silicon dioxide (Aerosil R972) and magnesium stearate were added as glidant and lubricant, respectively. All the drugs were micronized ($< 10$ $\mu$m) on an air jet mill (Fryma-JM80, Rheinfelden, Switzerland) in order to reduce particle size effects on the release rate.

*Drug solubility and wettability assessment*

The solubility of each drug was determined at 25 °C in phosphate buffer BP, pH 6.5, the same medium employed in the dissolution test. Excess powdered drug (1.5 g) was dispersed in 25 ml buffer and shaken for 72 h. An aliquot of the supernatant solution was filtered from the suspension by positive pressure at 25 °C and the filtrate, after appropriate dilution, assayed spectrophotometrically. Three determinations were made and the average solubility value calculated.

Contact angles of the micronized powdered drugs with triple distilled water were determined 2 weeks after milling. Two techniques were used: the maximum height of a drop on a presaturated compact (Kossen and Heertjes, 1965) and the Wilhelmy gravitational technique (Buckton, 1990). Results quoted are averages from five separate compacts and plates.

*Granule preparation*

100 g batches of the micronized drugs and appropriate amounts of Emvelop, Carbopol and Avicel powders to give drug/matrix ratios of 0.5, 0.666, 1.0, 1.5 and 2 were mixed by 10 min tumbling and then in a planetary mixer (Hobart N-50, Ontario, Canada) for another 10 min at a speed of 150 rpm. The proportions of the matrix forming components (Emvelop, Carbopol and Avicel) were kept constant at 7 : 2 : 1. Isopropanol was added at a slow steady rate to the blended mixtures by using a separating funnel over 10 min. The volume of the isopropanol added was dependent on the composition of the powder mixture. The plastic wet mass was cut into small pieces, dried for 24 h at 40 °C and passed through a granulator (Erweka Type FAG, Frankfurt, Germany) and then through a 0.7 mm sieve. Silicon dioxide 3% (w/w) and magnesium stearate 1.5% (w/w) were then added and tumbled mixed for 5 min.

*Tablet preparation and testing*

Granulations were compressed on an instrumented single-punch tableting machine (Manesty Type F3, Liverpool, U.K.) using a 10.5 mm diameter punch and die set at pressure levels of 5, 10, 15, 20 and 30 kN, to produce tablets with nominal strength of 100 mg of drug.

The tablets were weighed ($\pm 0.1$ mg) and their thickness and diameter measured ($\pm 0.01$ mm). The maximum force transmitted by tablets before they broke in tension was measured using diametral crushing. Packing fraction ($p_f$ = bulk density/true granule density) was calculated and tensile strength estimated by applying the relationship used by Fell and Newton (1970). True granule density was measured by an air comparison pycnometer (Beckman Model 930).

A dissolution test was carried out on three tablets from each formulation using USP Method II at stirring speeds of 50–250 rpm. The dissolution medium was 1000 ml of phosphate buffer BP, pH 6.5, containing 0.02% Tween 80 to ensure sink conditions. Absorbance measurements were taken up to 8 h using wavelengths of 322, 265 and 308 nm for indomethacin, ibuprofen and diclofenac, respectively.

## Results and Discussion

The results from the solubility and contact angle determinations are given in Table 1. Diclofenac is the most soluble and wettable. The

TABLE 1

*Solubility and wettability (contact angle) of powdered drugs*

| Drug | Solubility $C_s$ (mg ml$^{-1}$) (±S.E.) | Contact angle ($\theta°$) | |
|---|---|---|---|
| | | Drop height (±S.E) | Wilhelmy plate (±S.E) |
| Diclofenac sodium | 13.90±0.40 | 32±5 | 33±3 |
| Ibuprofen | 1.44±0.05 | 73±3 | 68±4 |
| Indomethacin | 0.16±0.01 | 69±3 | 63±4 |

wettability of ibuprofen and indomethacin is similar but their solubilities differ by one order of magnitude.

The effect of drug/matrix ratio on the release from tablets compressed at 10 kN and tested at 50 rpm is shown in Fig. 1(a–c). It is seen that indomethacin tablets with a drug/matrix ratio of 2 exhibit the most prolonged release and ibuprofen tablets with a drug/matrix ratio of 0.5 the fastest. The release rate increased with drug/matrix ratio for the diclofenac tablets but decreased for indomethacin and ibuprofen. Most of the release profiles in Fig. 1(a–c) are sigmoidal except for indomethacin tablets (drug/matrix ratio 2.0) and diclofenac (drug/matrix ratio 0.5), for which the release profiles are almost linear (zero order).

These contrasting effects may be caused by the action of the gel-forming carbopol as a binder in the presence of diclofenac but as disintegrant in the presence of the less wettable indomethacin and ibuprofen. The latter action is probably enhanced by the presence of the hydrophobic 'Emvelop'.

For the mixed hydrophobic/hydrophilic matrix system under investigation, drug release involves (a) penetration of the solvent into the matrix, (b) hydration and swelling of the hydrocolloid and dissolution of the active ingredients and (c) transfer of the dissolved drug and of soluble matrix components into the bulk solution. The Avicel draws up water into the tablets from the aqueous dissolution medium (wicking process) and carbopol takes up water, forms a gel and swells. The interaction between the carbopol and the other matrix materials (drug and Emvelop) determines the accommodation of the swollen carbopol. If the adhesion between the matrix components does not accommodate the swelling, deaggregation will occur. Therefore, the rate of matrix erosion (tablet deaggregation or dissolution of the swollen carbopol) and the rate of drug diffusion out of the gel formed, if any, will control the overall dissolution.

The log-linear plots of the percentage of undissolved drug vs time given in Fig. 2(a–c) show two parts. Initial release is followed by a faster phase (for all diclofenac tablets and indomethacin tablets

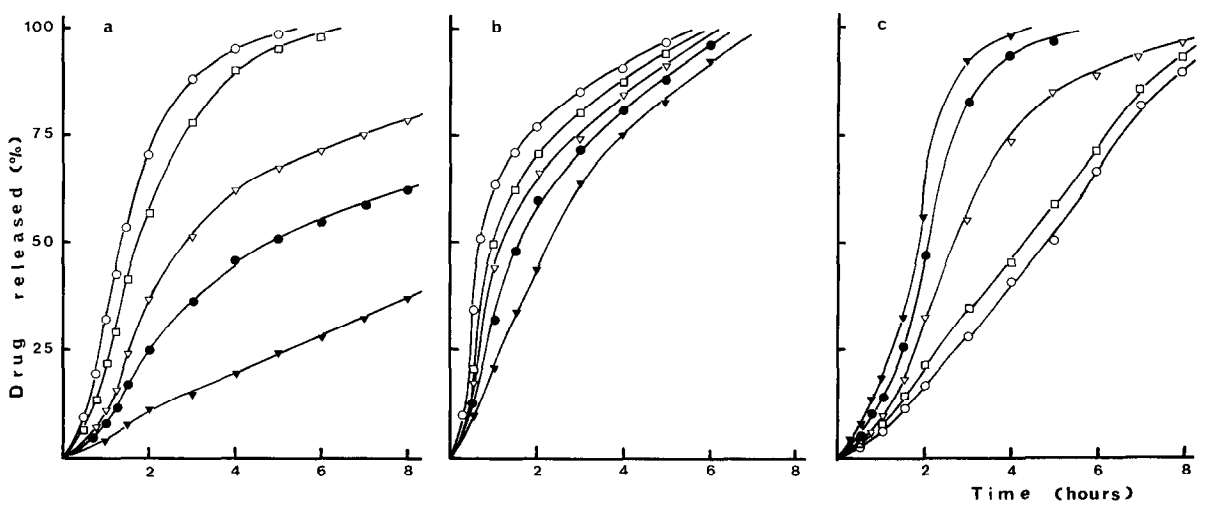


Fig. 1. (a–c) Release of drug from tablets (compressed at 10 kN and tested at 50 rpm) containing: (a) indomethacin (b) ibuprofen and (c) diclofenac sodium at different drug/matrix ratios: (○) 0.5, (□) 0.666, (▽) 1.0, (●) 1.5 and (▼) 2.

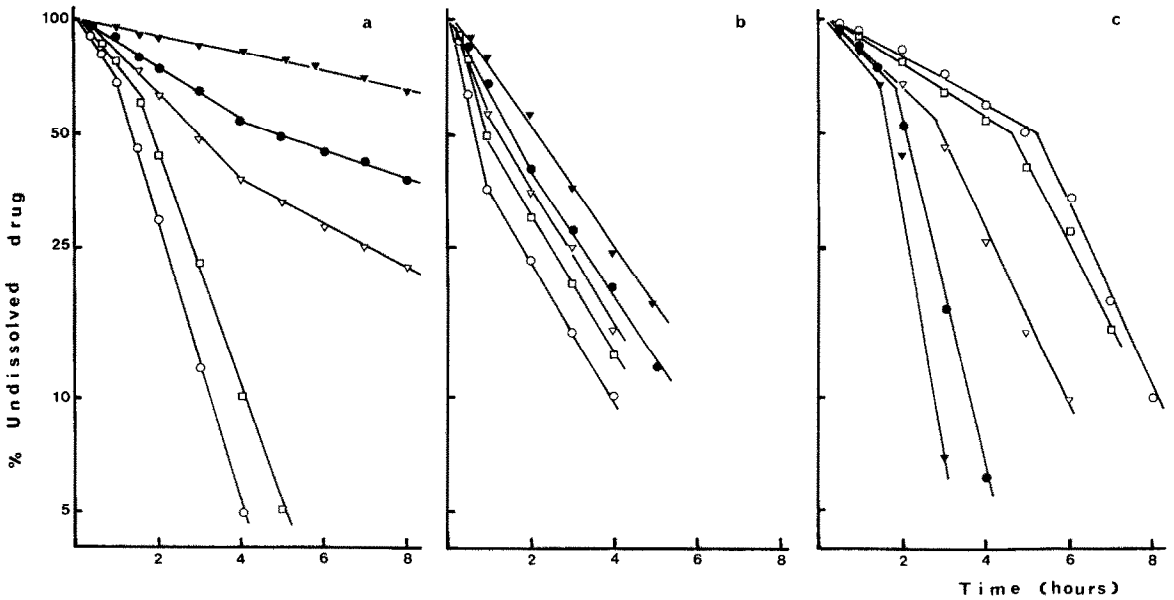


Fig. 2. (a–c) Percentage of undissolved drug vs time for tablets (symbols as in Fig. 1).

with drug/matrix ratio $< 1$) or by a slower one (for all ibuprofen tablets and indomethacin tablets with drug/matrix ratio $> 1$). The faster terminal release phase probably results from extensive erosion of the tablets, while the slower release may be obtained either when the diffusion of the drug through the gel of the hydrophilic carbopol has

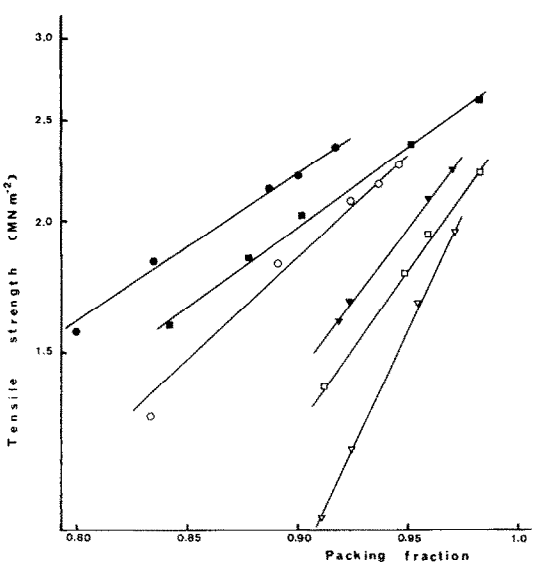


Fig. 3. Tensile strength vs packing fraction for tablets containing: (○) diclofenac sodium, (□) indomethacin and (▽) ibuprofen at drug/matrix ratio: 2 (solid symbols) and 0.5 (open symbols).

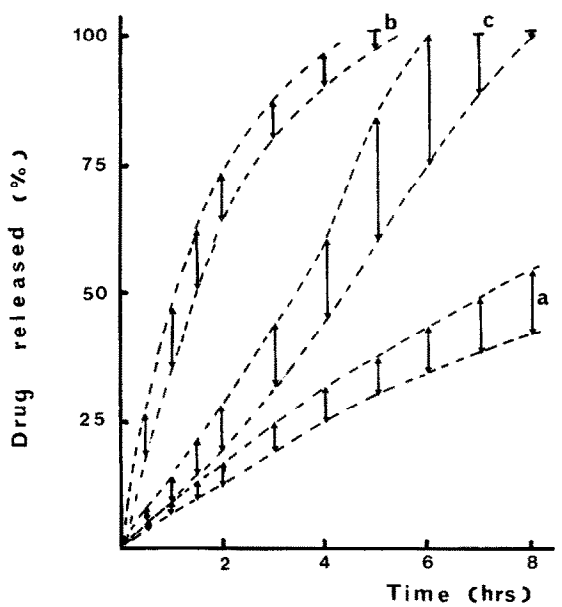


Fig. 4. Drug release from tablets compressed at different pressure (5–30 kN) and containing: (a) indomethacin (drug/matrix ratio 2), (b) ibuprofen (drug/matrix ratio 2), and (c) diclofenac sodium (drug/matrix ratio 0.5).

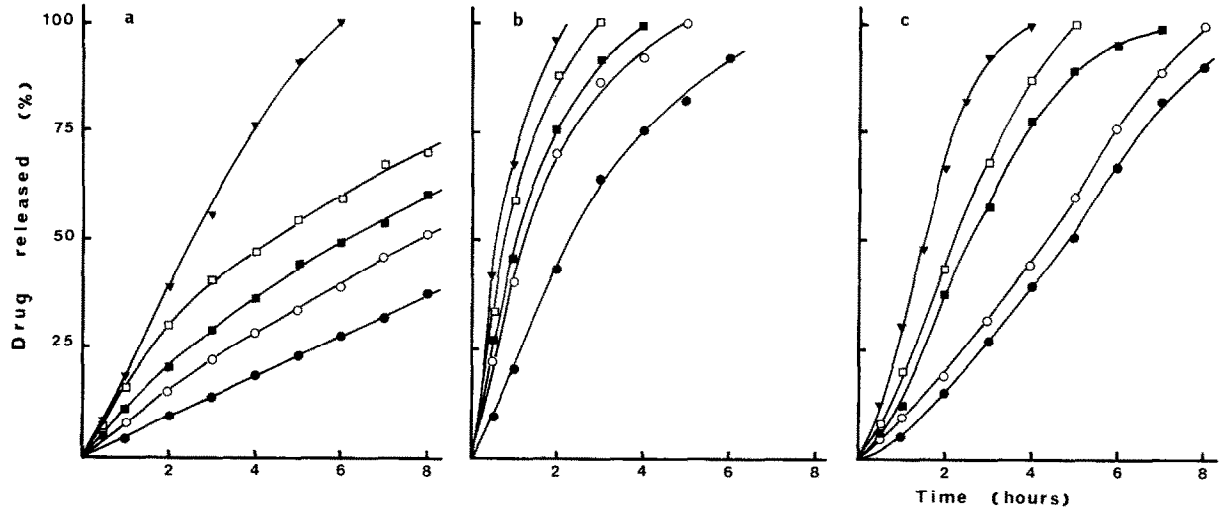


Fig. 5. Drug release from tablets compressed at 10 kN and tested at different stirring rate in the dissolution tester. Drug/matrix ratio: (a) indomethacin, 2; (b) ibuprofen, 2; and (c) diclofenac sodium, 0.5. Stirring rate: (●) 50, (○) 100, (■) 150, (□) 200 and (▼) 250 rpm.

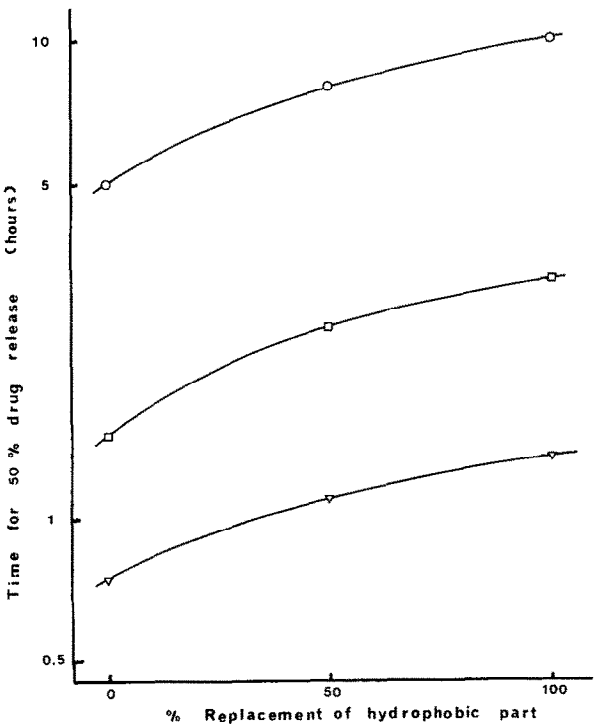


Fig. 6. Effect of gradual replacement of unwettable Emvelop by wettable Emcompress on the release, for tablets containing: (○) diclofenac sodium, (□) indomethacin and (▽) ibuprofen at drug/matrix ratio 0.5.

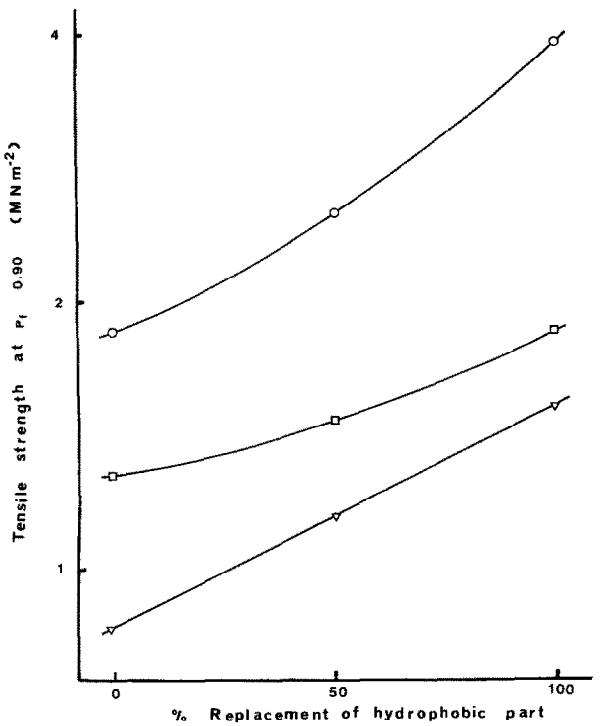


Fig. 7. Effect of gradual replacement of unwettable Emvelop by wettable Emcompress on the tensile strength of tablets (symbols as in Fig. 6).

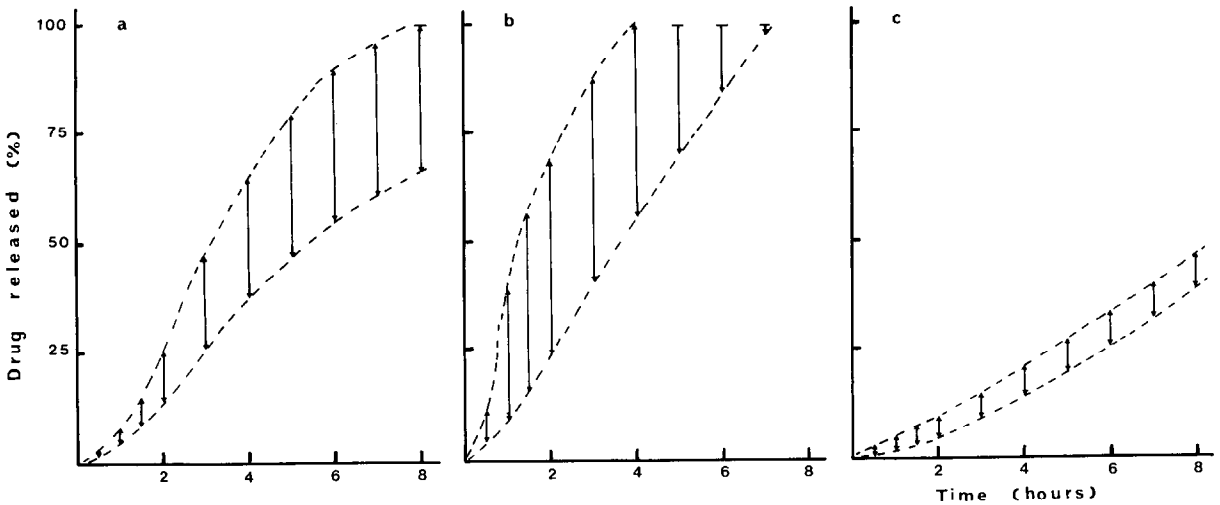


Fig. 8. Drug release from tablets compressed at different pressure (10–30 kN) after the replacement of unwettable Emvelop by wettable Emcompress (drug contained: (a) indomethacin, (b) ibuprofen and (c) diclofenac sodium at drug/matrix ratio 0.5).

become predominant (indomethacin tablets with drug/matrix ratio $> 1$) or after tablet deaggregation is complete (all the ibuprofen tablets).

Since adhesion and the interaction between the matrix components can be related to the rate of erosion in the presence of water and to the tensile strength of the tablets (Malamataris and Pilpel, 1982; Rowe, 1990), correlation between the drug release and the tensile strength was sought. Plots of log tensile strength vs packing fraction, $p_f$, were obtained and were, as expected (York and Pilpel, 1973), straight lines over the range of packing fraction 0.8–0.98. The values of the tensile strength at a fixed $p_f$ increased with increase in the drug/matrix ratio for all three drugs under investigation. Fig. 3 shows representative plots for the formulations with the higher and lower drug/matrix ratio. It is seen that variations in tensile strength correspond to the order of wettability of the incorporated powdered drugs. This may be explained by the relation between wettability (contact angle), spreading coefficient or free surface energy of the powdered materials and their interparticle binding during granulation and tableting (Malamataris and Pilpel, 1982; Rowe, 1990). But, despite the dependence of tensile strength on the compression pressure and packing fraction (Fig. 3), drug release was almost pressure independent (Fig. 4). Furthermore, release rate was found to be affected greatly by the stirring conditions during dissolution (Fig. 5).

The independence of release from compression pressure and packing fraction and dependence on stirring rate during dissolution indicate that, for the formulations under investigation, the penetration of the liquid into the matrix has less effect on the drug release prolongation than the transfer of the drug from the matrix into bulk solution due to detachment of aggregates (disintegration) or dissolution of the gel formed (erosion).

To check further the effect of the powder wettability on the release prolongation, the unwettable, insoluble and hydrophobic part of the matrix (Emvelop) was replaced by a wettable, insoluble component of similar particle size Emcompress (125 $\mu$m). Figs 6 and 7 show the effect of gradual replacement of Emvelop on the time for 50% drug release and the tensile strength at fixed $p_f$ 0.9, respectively. It is seen that the tensile strength increases and release is prolonged. The release is also more pressure and porosity dependent (Fig. 8).

This study shows that the combination of diffusion and erosion release mechanisms in a matrix system comprising an insoluble hydrophobic and a hydrophilic gel-forming part depends greatly on the wettability of the added drug. Furthermore, with wettable and water soluble drugs, the matrix

swells and release is mainly achieved by diffusion and erosion due to dissolution of the gel formed. However, with less wettable drugs, the matrix erodes, due to deaggregation caused by the inability of the matrix to accommodate the swelling of the gel forming hydrophilic part. Further investigation on the adhesion of high molecular weight, gel-forming materials to hydrophobic or hydrophilic drug surfaces is needed, for the prediction of the balance between the diffusion and erosion release mechanism, in sustained release matrix systems comprising hydrophobic and hydrophilic, gel-forming, components.

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