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Encapsulation and in vitro release of indomethacin from semi-solid matrix capsules

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Summary

Indomethacin 50 mg was blended with semi-synthetic glycerides (Suppocire) having lipophilic (Type AM) and hydrophilic (Type BP) properties, and encapsulated into hard shell gelatin capsules. A vehicle comprising a 1 : 1 binary mixture made up of bases AM and BP was also investigated with regard to in vitro release of indomethacin from the encapsulated semi-solid. Release from the AM base (% $Rel_{60\ min} = 13.5$) seemed to occur by an erosion process, whereas that from the BP base appeared to occur via a diffusion-controlled mechanism (% $Rel_{60\ min} = 87.9$); 89.8% of indomethacin was released from the binary mixture after 6 h. No correlation was observed between the melting points of the respective indomethacin–base mixtures and the rate of drug release.

Introduction

Hard shell gelatin capsules are containers for a diversity of fill materials ranging physically from solids to semi-solids and liquids. Thermosetting semi-solid matrix fills offer many advantageous features over conventional powder fills. Besides facilitating the filling of the capsule shell with excellent fill weight and content uniformity while minimising problems associated with dust control of hazardous substances, they also offer protection against environmental influences with minimal consequences of hydrolysis and oxidation of the dispersed or dissolved active principles (Jones, 1985). It is also probable that semi-solids which are thermosoftening at body temperature may have the tendency to spread more readily and disperse their contents, thus preventing the effects of localised irritation of the mucus membrane of the oesophageal-gastro tract caused by dose-dumping of ulcerogenic drugs.

It has been claimed (Jones et al., 1988) that the semi-solid matrix offers a low-cost alternative to produce formulations which modify drug release. This may be achieved by controlling the drug's diffusion rate which can be changed by altering the nature of the base by changing the HLB value and the melting point, or by using combinations of bases, as the more hydrophobic the base the slower the release rate of the drug and vice versa.

Several inert semi-solid thermosetting excipients (Francois and Jones, 1979) such as animal, mineral or vegetable waxes, as well as semi-synthetic waxes and mixed esters commonly used as suppository bases with varying hydrophilic and lipophilic properties and melting points, are avail-

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able, and may be considered for encapsulation. Suppocire bases used in this investigation as vehicles for encapsulation, are derived from transesterified vegetable oils and are characterised according to their melting points and level of hydroxyl groups present.

Materials and Methods

Capsule fill formulations

Mixtures containing Suppocire (Gattefosse) bases Types AM (hydroxyl value < 6) (Formulation 1) and BP (hydroxyl value 30–50) (Formulation 2), and a 1 : 1 combination of these bases (Formulation 3), each containng sufficient indomethacin to yield capsules (hard gelatin size 0) of average weight 0.75 g and containing 50 mg of indomethacin, were prepared by melting the respective bases at 45 °C (unless otherwise specified) followed by trituration with the indomethacin. The molten mixtures were filled manually into capsule shells and allowed to set at 20 °C for 24 h.

Melting point determinations on indomethacin, bases AM and BP, as well as their formulations prepared at 45, 55 and 80 °C, were performed by the capillary tube method using a Gallenkamp apparatus.

Disintegration tests

Tests were performed according to the U.S.P. XXI using an Erweka ZT6 disintegration tester without discs, in water at 37 °C.

Dissolution tests

In vitro release of indomethacin was determined using the U.S.P. rotating basket method (Pharma Test Type PTW S) at 100 rpm in phosphate buffer dissolution medium (pH 7.2) at 37 °C. Indomethacin determinations were done by UV-spectroscopy at 318 nm. (Base materials were found to exhibit negligible absorbance.)

Results and Discussion

The semi-solid bases used had different hydrophilic–lipophilic properties but closely similar melting points. Bases AM and BP having hydroxyl values of below 6 and 30–50, respectively, were found to have melting points of 35–36.5 °C and 35–37 °C, whereas the combination base AM/BP(1 : 1) melted at 34–35 °C. The inclusion of indomethacin as expected, had a slight lowering effect on the melting point of the respective compositions as shown in Table 1. From Table 1 it may also be seen that very little change in the melting points of indomethacin formulations occurred when prepared at higher temperatures. However, a dark yellow discolouration due to possible degradative changes resulted on addition of the indomethacin to the base at 80 °C.

TABLE 1

Melting points of thermosetting bases and formulations prepared at different temperatures [a]

Preparation temperature (°C)	Base/Formulation	Melting point (°C)
–	AM	35–36.5
–	BP	35–37
45	AM : BP 1 : 1	34–35
45	Indomethacin [b] 10% m/m in AM base	33–34
55	as above	34–34.5
80	as above [c]	33–34
45	Indomethacin 10% m/m in BP base	33–34
55	as above	34.5–35
80	as above [c]	34.5–35
45	Indomethacin 10% m/m in AM/BP 1 : 1 base	33.5–34

[a] Temperature at which base was melted prior to incorporation of indomethacin.
[b] Melting point of indomethacin: 158–160 °C.
[c] Discolouration occurred.

The encapsulated mixtures of Formulations 1, 2 and 3 disintegrated readily, requiring an average time of 4.5 min. The disintegration times recorded were those taken for the contents to melt in the water at 37 °C once the capsule shell had started to dissolve. Formulations 1 and 3 containing the hydrophobic AM base did not disperse readily throughout the disintegration test medium. However, the BP base contained in Formulation 2 mixed easily throughout the water due to its hydrophilic nature. The fact that this base liquifies at

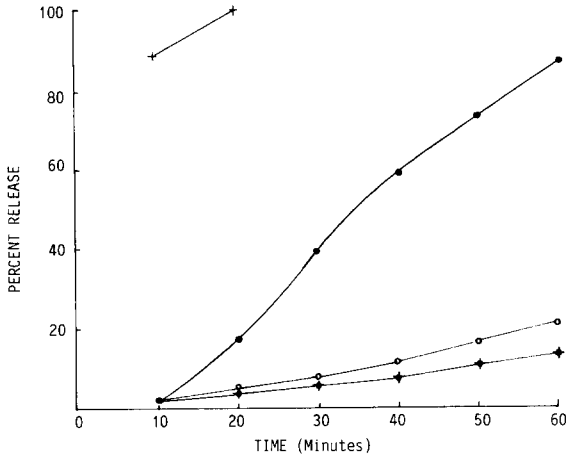

Fig. 1. Dissolution–time profiles for indomethacin release from Formulation 1 (AM base) (◆); Formulation 2 (BP base) (●); Formulation 3 (AM:BP base 1:1) (○); Indocid 50 mg capsules (+).

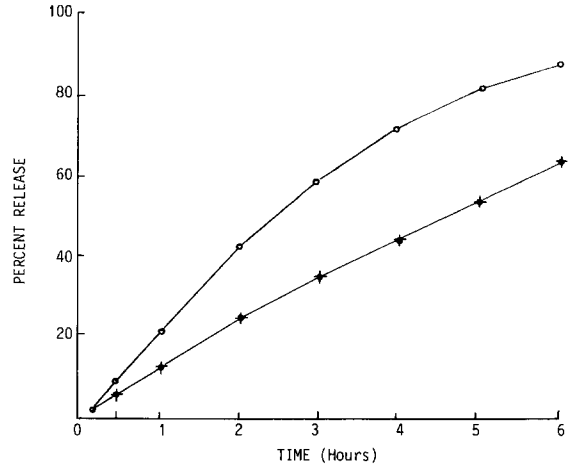

Fig. 2. Dissolution–time profiles for indomethacin release from Formulation 1 (AM base) (◆) and Formulation 3 (AM:BP base 1:1) (○) over a 6-h period.

body temperature has the added advantage that if after swallowing, the capsule became lodged within the oesophagus, it would disintegrate and the liquified contents be easily dispersed.

Dissolution studies indicated that the amount of indomethacin released after 60 min was 13.5%, 87.9% and 21.4% from Formulations 1, 2 and 3, respectively (Fig. 1). By contrast, indomethacin released from Indocid 50 mg (MSD) capsules containing a powder fill was rapid, with total release being observed after 20 min. Drug release from a semi-solid matrix may occur by diffusion or erosion or both. With a diffusion-controlled release mechanism, release should be proportional to the square-root of time (Higuchi, 1963). When release occurs through gradual erosion of the matrix, the Hixson–Crowell cube-root law (1977) of dissolution is likely to prevail (Carstensen, 1977). The slow release from Formulation 1 which released 62.4% of indomethacin after 6 h (Fig. 2) is attributable to its hydrophobic nature. Release was in accordance with the Hixson–Crowell cube-root law for drug dissolution (Fig. 3), and thus occurred predominantly through an erosive mechanism. The base upon melting did not disperse readily, and was observed to become impacted within the rotating basket. A similar phenomenon occurred with Formulation 3. Release from Formulation 2 which contained the hydrophilic BP base seemed to occur via a diffusion related mechanism after 20 min and over the first hour, when release became proportional to the square-root of time (Fig. 4). In this instance, a high degree of

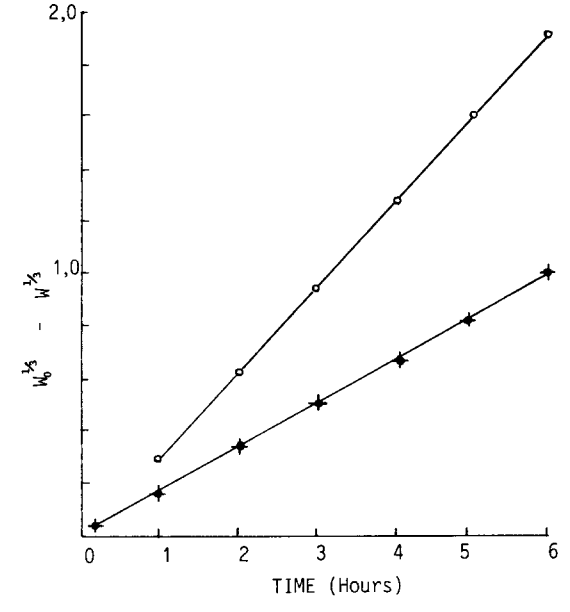

Fig. 3. Hixson–Crowell * plots of Formulation 1 (AM base) (◆) and Formulation 3 (AM:BP base 1:1) (○).
* W_0 = amount of drug in capsule; W = amount of drug remaining in matrix after dissolution.

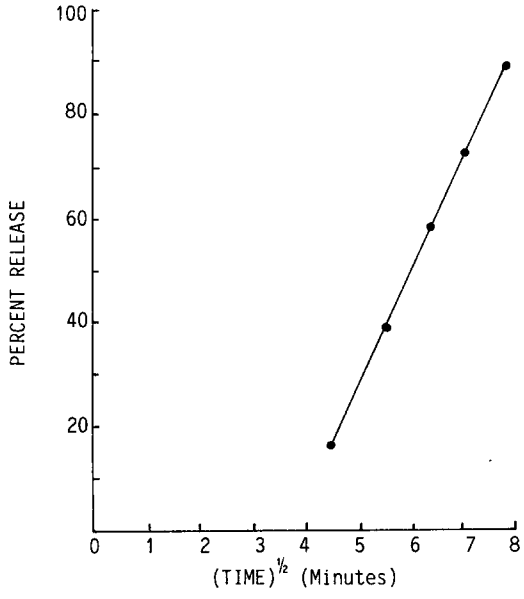

Fig. 4. Diffusion-controlled indomethacin release from Formulation 2 (BP base), over a 60-min period.

base dispersion occurred in the dissolution medium, and was accompanied by the formation of an oily layer and scum on the surface.

It is likely that drug release from semi-solid matrices could occur not only by diffusion or erosion, but biphasically through a diffusion and erosion process. Release through erosion appeared to occur after one hour in the case of indomethacin release from the binary mixture (Fig. 3) (Formulation 3), and was found to be 89.8% after 6 h (Fig. 2). Initial release, however, could have occurred predominantly through a diffusion-related mechanism due to the presence of a hydrophilic component (BP base) in the base mixture.

An investigation of salicylic acid and tioconazole release from thermosetting fatty vehicles (Howard and Gould, 1987) indicated that release of the former was related to the vehicle HLB, but in the case of the latter a similar relationship could not be identified, as lipophilic drugs require a rapidly eroding vehicle to achieve levels suitable for oral sustained release dosing. Drug release from these vehicles is thus not a simple function of vehicle HLB. A predictive relationship between the hydrophilic–lipophilic properties of the base and drug release may thus also be drug-dependent.

An in vitro study of indomethacin release from suppositories (Othman and Muti, 1986) revealed that the rate of release of indomethacin was unexpectedly higher from oily bases with low hydroxyl values. This was attributed to the pH of the test medium which allowed 99.9% ionization at pH 8.0. However, the presence of surface-active agents in the series of bases investigated, and the influence of the solidification points of the bases were considered. Although the solidification point appeared to have a significant role in drug release from suppositories it is of interest that the Suppocire bases AM and BP used in the present investigation had closely similar melting point ranges but widely different in vitro drug release capabilities, with no observable correlation between melting points of the respective indomethacin-base mixtures and release of indomethacin.

Conclusion

The formulation potential of thermosetting vehicles for the encapsulation of drugs offers several advantageous applications, most of all a means of controlling drug release, provided the nature of such vehicles is fully understood and the limitations of an in vitro evaluation appreciated. The encapsulation of indomethacin in this regard may offer benefits of effective in vivo availability and possible protection against irritation after oral administration. These prospects need further investigation to realise the full potential of semi-solid matrix capsules.

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