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Note

The effects of pressure and direct compression on tabletting of microsponges

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Abstract

Microsponges are porous, polymeric microspheres that are used mostly for topical and recently for oral administration. Ketoprofen was used as a model drug for systemic drug delivery of microsponges in the study. Ketoprofen microsponges were prepared by quasi-emulsion solvent diffusion method with Eudragit RS 100 and afterwards tablets of microsponges were prepared by direct compression method. Different pressure values were applied to the tablet powder mass in order to determine the optimum pressure value for compression of the tablets. Results indicated that microsponge compressibility was much improved over the physical mixture of the drug and polymer and owing to the plastic deformation of sponge-like structure, microsponges produce mechanically strong tablets.

Keywords: Microsponges; Modified release; Ketoprofen; Direct compression

Ketoprofen [2-(3-benzoylphenyl) propionic acid] is a non-steroidal anti-inflammatory (NSAI) drug which has been widely used in clinical practice. Following oral administration of regular release preparations, ketoprofen is rapidly absorbed with peak concentrations occuring between 0.5 and 2 h after the dose and it has a short half life in plasma about 1–3 h (Borsa et al., 1983; Dennis et al., 1985; Oka and Aoshima, 1985; McCrea et al., 1986; Ollagnier et al., 1987; Foster et al., 1988; Jamali and Brocks, 1990). Ketoprofen causes gastrointestinal (GI) side effects like other NSAI drugs (Thomas and Kantar, 1986). The present study was designed to improve ketoprofen's pharmacokinetic properties and reduce GI side effects by means of microsponge system. In the first step, microsponges of ketoprofen were prepared and in the second step, the effects of pressure on the compressibility of the microsponges were investi-

Table 1
Composition of microsponges

Internal phase		External phase	
Ketoprofen	0.288 g/ml	Distilled water	200 ml
Ethyl alcohol	10 ml		
Eudragit RS 100	0.096 g/ml	PVA	0.2 g/ml
TEC	0.0192 g/ml		

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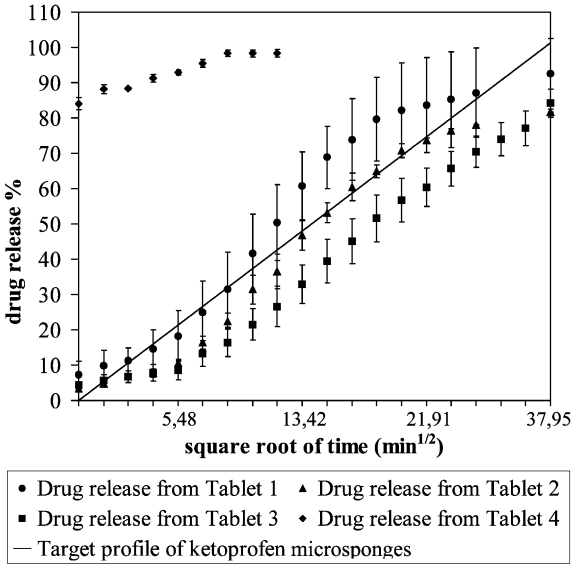


Fig. 1. Release profiles of ketoprofen from tablets containing different amounts of Precirol.

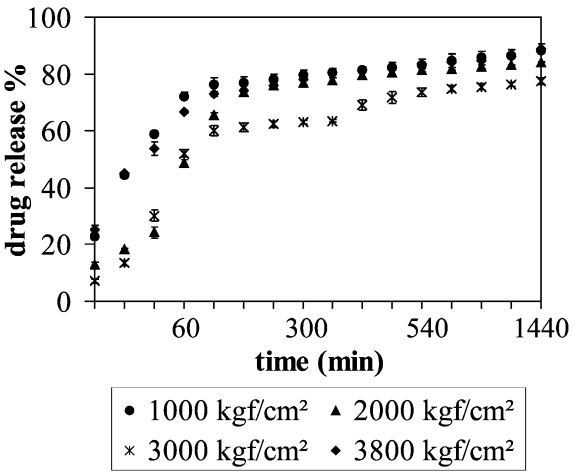


Fig. 2. Release profiles of ketoprofen from Tablet 2 compressed at different pressure values.

gated. In a study in vitro characteristics of the prepared microsponges were investigated and evaluated (Çomoğlu et al., 2000a).

Microsponges were prepared by quasi-emulsion solvent diffusion method (Barkai et al., 1990; El Khodairy et al., 1992; Wan et al., 1992; Kawashima et al., 1993; Akbuğa and Durmaz, 1994; Çomoğlu and Gönül, 2000b) using an external phase of containing 200 ml distilled water and 40 mg polyvinyl alcohol (PVA) 72.000. The internal phase consisted of ketoprofen, ethyl alcohol, polymer and triethylcitrate (TEC) which was added at a quantity of 20% of the polymer in order to facilitate the plasticity of the polymer. Composition of the microsponges is given in Table 1.

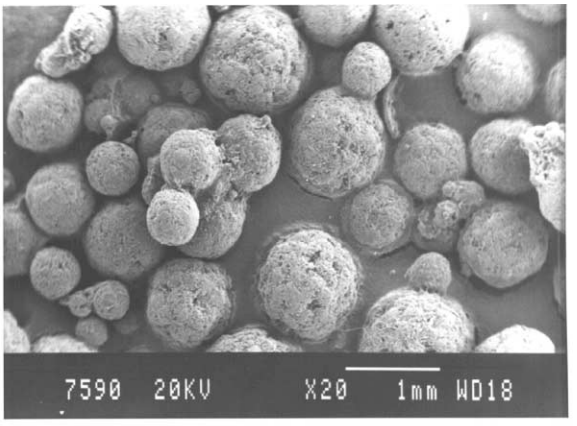
Table 2
Composition of tablets

Formula	Composition			
	FlowLac® 100 (mg)	Precirol® (mg)	Microsponges[a] (mg)	Total weight of tablet (mg)
Tablet 1	91.525	1.5	206.975	300
Tablet 2	90.025	3	206.975	300
Tablet 3	87.025	6	206.975	300

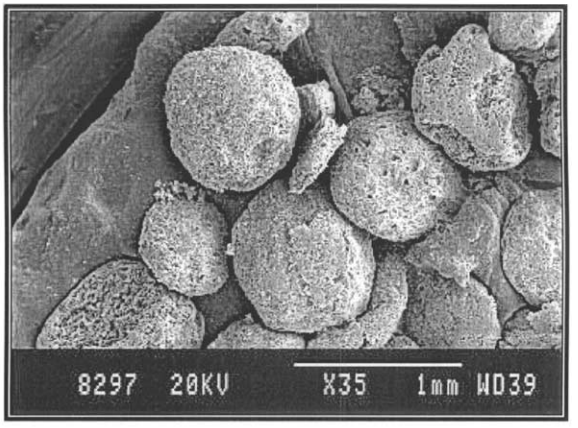
[a] Each tablet formulation contains 200 mg of encapsulated ketoprofen.

Table 3
Composition of the tablet containing physical mixture of the drug and the polymer

Formula	Composition				
	FlowLac® 100 (mg)	Precirol® (mg)	Ketoprofen (mg)	Eudragit RS 100 (mg)	Total weight of tablet (mg)
Tablet 4	90.025	3	200	6.975	300

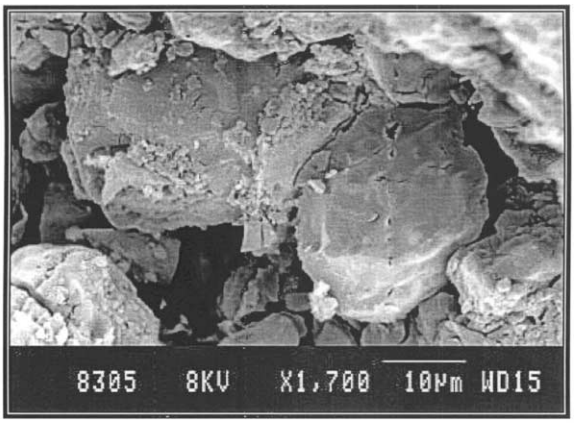


(A)

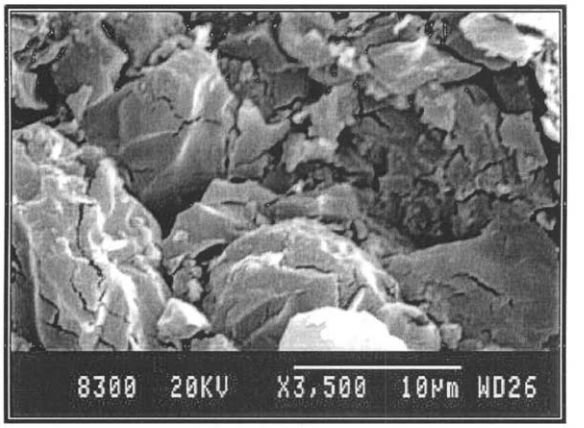


(B)

Fig. 3. Scanning electron microphotographs of microsponges (A) before (B) after dissolution test.



(A)



(B)

Fig. 4. Scanning electron microphotographs of Tablet 2 pressed with (A) 1000 kgf/cm^2 (B) 3800 kgf/cm^2 pressure.

Table 4
f_2 (similarity) test results of Tablets 1, 2 and 3

Applied formula	f_2 (similarity) test results (%)	Interpretation
Tablet 1 to 2	50.11	Tablet 2 similar to Tablet 1 at 50.11% level
Tablet 1 to 3	38.41	Tablet 3 different from Tablet 1 at 38.41% level
Tablet 2 to 3	54.49	Tablet 3 similar to Tablet 2 at 54.49% level

First of all, the internal phase was prepared at 60 °C and then added to the external phase at room temperature. After emulsification, the mixture was continuously stirred for 2 h. Then it was filtered to separate microsponges, and dried by vacuum oven for 24 h. The product was weighed and separated into size fractions using standard sieves.

Trials to compress the microsponges into tablets without additives were not successful, for this reason, several tablet formulations were prepared by direct compression with FlowLac® 100 and different percentages (0.5, 1, 2%) of Precirol®(Fig. 1). Tablet formulations were composed

according to Table 2 and Table 3. All tablets were prepared by using a 10 mm flat-faced punch and hydraulic press.

During the tabletting process, compression properties of ketoprofen microsponges were investigated. It was assumed that the microsponges might possess an unique compression property due to their matrix or sponge-like structure which differed from conventional microcapsules or physical powder mixture (Kawashima et al., 1992). Different compression pressures (1000, 2000, 3000, 3800 kgf/cm^2) were applied to the tablets and results were evaluated by both SEM and in vitro release rate studies.

In vitro release rate studies on tablets were carried out by paddle method specified in USP XXIII. They were placed in pH 7.4 phosphate buffer solution at 37 °C and rotated at 50 rpm. Ketoprofen amount in withdrawn samples was determined by spectrophotometrically at 262 nm (Schimadzu, UV–VIS 1202).

It was determined that because of their sponge-like texture microsponges can easily be compressed by direct compression and can be applied by oral route for systemic drug delivery. Among the four tablet formulations Tablet 2 seemed to be the best formulation because when release profiles compared (Figs. 2 and 3), Tablet 2 followed the closest profile to the target profile, and in addition this result was supported by f_2 (similarity) test which was applied to Tablets 1, 2 and 3 (Table 4). Tablet 1, 2 and 3 all modified the release of ketoprofen when they were compared with drug itself and physical mixture of drug and polymer. When the correlation between release rate and pressure was examined, it was observed that they were reversely proportional to each other for 2 h, after that time polymer swells and diffusion pathway gets longer so drug release seems to be equal except for 3800 kgf/cm^2 pressure. When this amount of high pressure was applied, it was determined that drug release increased, although pressure was at the highest value. It can be explained by structure deformation of microsponges which can be seen in Fig. 4B. Therefore, 1000–2000 kgf/cm^2 pressure can be applied for compression of microsponge tablets.

Microsponge tablets containing ketoprofen appear to be a suitable dosage form for oral application. Preliminary drug release tests of the tablets prepared with microsponges exhibited typical drug release profiles characterized by the Higuchi-matrix model. Further investigations are being made.

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