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The Efficiency Of Glyceryl Behenate As Sustained-Release Agent Compared With Hydroxypropylcellulose In Tablets

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Abstract: The aim of this study was to compare the in vitro release of theophylline between matrix tablets containing glyceryl behenate (Compritol 888 ATO®) traditionally used as lubricant and tablets containing hydroxypropylcellulose (HPC) largely used as hydrophilic matrix. It was observed that matrix diffusion-controlled mechanisms of drug release from the two matrixes were operative. When the matrix consisted only of Compritol 888 ATO®, the drug release followed Fickian diffusion while it followed non-Fickian diffusion when hydroxypropylcellulose was alone used. In both cases, a drug sustained-release was observed. On the other hand, tablets prepared with varying mixtures of these two matrixes followed Fickian diffusion only, which suggested that the influence of Compritol 888 ATO® masked that of HPC during the drug release. However, the comparative analysis of the obtained data suggest that Compritol 888 ATO® may be recommended as a matrix agent in the development of sustained release formulation in spite of its traditional role as a lubricant.

Keywords: theophylline, HPC, Compritol 888 ATO®, polymer mixtures, matrix tablets, drug delivery system.

Introduction

Glyceryl behenate (Compritol 888 ATO®) is a lipophilic excipient traditionally used as a lubricant for direct compression and as an aid to filling hard capsule tablets[1,2]. During the past few years, it has been used as a lipophilic matrix to achieve controlled release dosage[3-8]. El-Sayed et al[9]. showed that the drug release profiles of tablets containing these excipient as a matrix agent were best described by the linear square root of

time dependence indicating a diffusion controlled mechanism. On the other hand a number of hydrophile matrixes such as hydroxypropyl ethyl cellulose (HPEC), hydroxypropyl methylcellulose (HPMC), Hydroxypropylcellulose (HPC), sodium carboxyl methylcellulose (SCMC) and polyvinylpyrrolidone (PVP) were used as classical excipients to control dissolution rates from sustained-release[10-14]. A further point to consider is relative to the effects of hydrophilic-hydrophobic properties (HPC-Compritol 888 ATO®) on drug delivery system. The aim of this study was to compare the in vitro drug release between matrix tablets containing Compritol 888 ATO® and hydroxypropylcellulose largely used as hydrophilic matrix.

Experimental

Glyceryl behenate (Compritol 888 ATO®, Gattefossé, France) and hydroxypropylcellulose (HPC-GF, Hercules, Inc, USA) were used as the matrix. Theophylline monohydrate (Cooper, France) was the used drug and Talc was used as lubricant (Cooper, France). Tablets of 125 mg containing 20 % of theophylline monohydrate were obtained according to the following formulas (Table 1).

The thermal analyser DTA-TG (Setaram 92 France) with platinium thermocouple was used in this study. The heating rate was 2 °C min^{-1} from ambient temperature up to 300 °C. The kaolin powder was chosen as a reference for its thermal stability. Twenty-five mg of mixture was used in each assay, realised under air sweeping *(0.5l h^{-1}).* The mixtures of theophylline, Compritol 888 ATO® and HPC-GF were prepared by mixing theophylline (20%) with various ratios of Compritol 888 ATO® and HPC-GF total (80%). In the case of various Compritol 888 ATO®/HPC-GF combinations (80%), the concentration of Compritol 888 ATO® were 0, 20, 50, 80, and 100%.

A non-aqueous granulation process was adapted to prepare HPC and Compritol granules. All powders were mixed, except talc, in a mixer granulator (GUEDU, France) during 4 min. Alcohol was used as the granulating liquid. The granules obtained were dried in an oven at 60 °C for 5 hours. After drying, the granules were calibrated using a ERWEKA oscillating granulator, (sieve 1mm/0.65), and lubricated with 2% m/m talc in a Turbula mixer (T2C, Willy A. Bachofen AG, Switzerland) at 60 rpm for 10 min. Tablets were compressed using a single punch tablet press (FORGERAIS, France) equipped with 7 mm flat-faced punch. Compression forces were adjusted to made tablets of the same thickness.

Mass and hardness of tablet formulations were determined by analytical balance (Mettler LP 12, Switzerland) and hardness tester (Erweka, Germany), respectively. The friability of these tablets was measured by friabilator (Erweka TAR, 40 rpm) for 15 min.

The dissolution test was carried out using the USP 23 apparatus 2. An automatic Pharma test PTW3C dissolution apparatus (Prolabo, France) was coupled to CamSpec M330 UV/Vis spectrophotometer with continuous flow to provide drug dissolution data. Six samples from each formulation were tested using 1000 ml of simulated gastric fluid (pH 1.2) at 37 °C and with stirring rate of 100 rpm. The drug was determined at 270.5 nm.

The method used to compare drug relaese was :

- the time parameter td of Webbul equation[15] which is the time it what 63.2% of the drug is disoslved.

In an attempt to elucidate the mechanism of drug release the dissolution data were plotted according to the Peppas equation[16],

The release kinetic data were computed using the following equation :

$$\ln M_t/M_\infty = \ln K + n \ln t$$

where M_t/M_∞ is the fractional release of drug in time t, K is the constant apparent, and n diffusional exponent. The value of n is 0.5 for fickian diffusion and 1 for diffusion II, the intermediate value of n between 0.5 and 1 indicates a non -fickian or anomalous diffusion which is a mixture of fickian and case II diffusion. When n is greater than 1 the drug release accrues through the super case II diffusion[16].

Table I: Formulation ingredients used and their amount

Formula	1	2	3	4	5
Theophylline (mg)	25	25	25	25	25
HPC GF (mg)	97.5	78	48.5	19.5	0
Compritol 888 ATO®(mg)	0	19.5	48.5	78	97.5
Talc (mg)	2.5	2.5	2.5	2.5	2.5

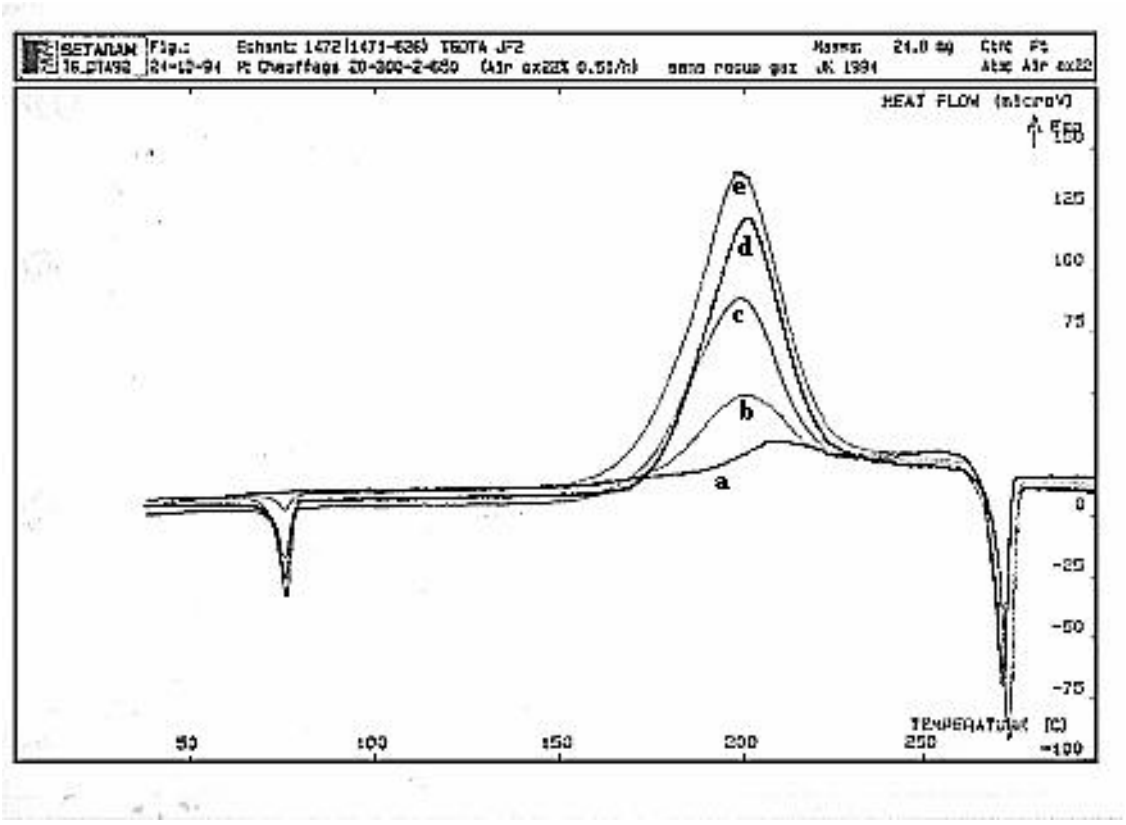

Fig. 1 : TG-DTA profiles of theophylline / matrixes mixture (20/80) :
Compritol 888 ATO Ġ : a) 0%, b) 20%, c) 50%, d) 80% and e) 100%

Table II: TG-DTA Characterisation of theophylline/matrixes mixture (80/20)

Formula	Endothermic peak melting (°C)	Exothermic peak (°C)	Endothermic peak melting (°C)
1	-	204	269
2	73	195	269
3	73	195	269
4	73	197	270
5	73	195	270

Results And Discussion

Fig. 1 and Table II show the DTA results. The thermal analysis until 280°C applied to pure ingredients gives the following results:

- Compritol 888 ATO®: maximun of the endothermic melting peak at 75°C; maximum first exothermic peak (oxidation accompanied by degradation) at 267°C.
- Theophylline: maximum of the endothermic melting peak at 274°C.
- Hydroxypropylcellulose: very small exothermic peak at about 167°C.

It was earlier shown a shift of the exothermic peak of Compritol 888 from 267 to 204 °C due to oxidization of the fatty acid ester, because of the presence of solid form in the interval 200 – 260 °C. An active drug with a melting temperature clown than 200 °C did not show any exothermic peak. In addition, Compritol 888 presents a better preservative effect versus other fatty acids matrices used in modified release formulation.

In our earlier study[18], a shift of the exothermic peak of Compritol ATO® from 267 to 204°C was observed for the binary mixture: Compritol 888 ATO®-Kaolin. The shift of this exothermic peak to lower temperature takes place only when the melting of the pure drug occurs higher than 200°C.

The observed temperatures listed in table II were determined with a maximum error of 1°C ± 73°C (melting of the Compritol 888 ATO®), 195-197°C (oxidation and degradation of Compritol 888 ATO®), 269-270°C (melting of the theophylline).

Table III: Physical characteristics of the tablets

Formula n°	1	2	3	4	5
Isopropyl alcohol (ml)	70	70	70	74	92
Wetting and Kneading time (mn)	9	7	8	7	7
Average Weight (mg)	125	128	125	130	127
Hardness(kp)	5.80	5.70	5.7	4.50	3.50
Friability (%)	0.01	0.30	0.32	0.52	0.70

The tablets' macroscopic evidence did not reveal any capping or sticking sign. In table III are indicated the physical characteristics. The hardness values ranged from 3.5 to 5.8 kp. These tablets were obtained by different compression forces used (results of which will be published later) to obtain tablets with same thickness. All the formulations studied produced tablets with good mechanical properties although the low hardness values of formulations 4 and 5 were observed. In all the cases friability of tablets was less than unite and satisfied the USP 23 requirement. It is worth noting to note that when the matrix consisted of HPC only, the amount of granulating liquid required was less important than that used when the matrix consisted of Compritol alone. The high solubility of HPC in the granulating liquid could partly explain this difference.

The dissolution test was used as a basis for evaluating the influence of different matrix combinations on the dissolution rates of theophylline. In order to simplify the comparative study, the release profiles were represented individually in Fig. 2. It can be observed that the drug release profiles depended on chemical characteristics of matrixes used. Fast release rate was observed with the formula containing only HPC compared to the formula containing only Compritol 888 ATO®. The latter produced slow release. After 8 h. 100% of the drug has been dissolved from HPC, while approximately 60% was released from Compritol 888 ATO®. This difference was attributed to the different hydrophilic-hydrophobic properties of both excipients. On the other hand levels of Compritol 888 ATO® resulted in similar release profiles. These data suggest that a hydrophobic additive slowed the release independently of the concentration of the hydrophobic compound. In order to clarify this situation it is worth considering the hardness data and amount of granulating liquid. These data recorded in Table III clearly illustrate that the formulas with low concentration of Compritol 888 ATO®

are of higher hardness and of lower friability compared to the formula containing only Compritol 888 ATO (Table III, formula 5). This may be explained by the effects of different amount of granulating liquid associated with the effect of hardness on the drug release.

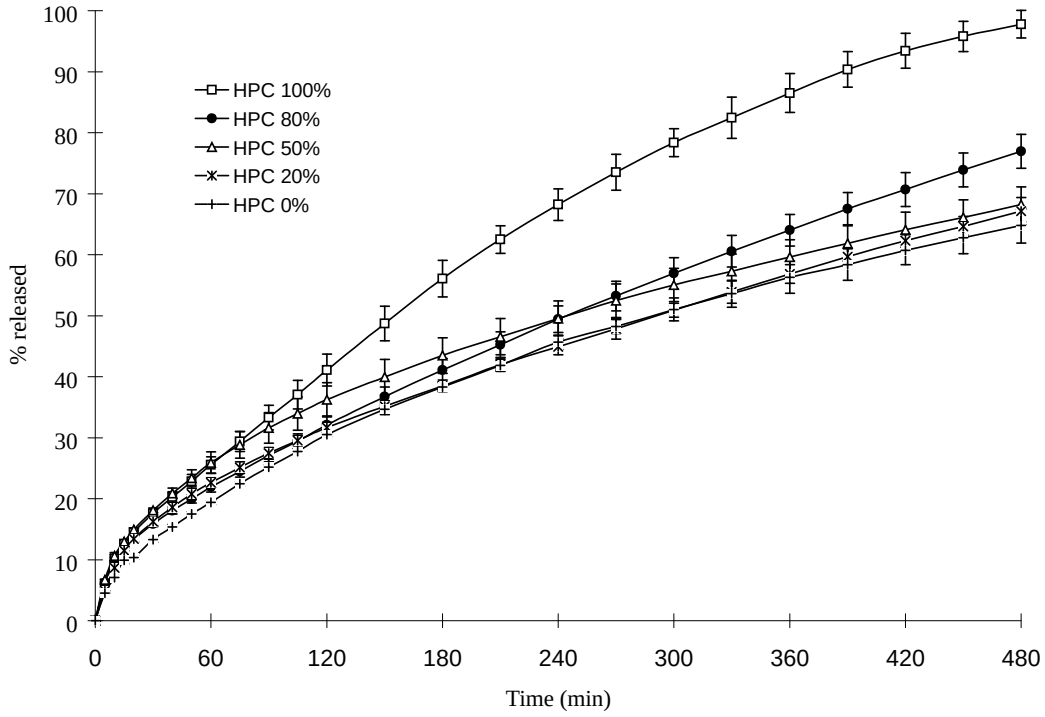

Fig. 2. Dissolution profiles of theophylline from tables with various matrixes (mean ± SD, n = 6 replicates)

Table IV: b and Td values parameters of Weibull and their correlation coefficients

Formula n°	1	2	3	4	5
b	0.93	0.78	0.61	0.66	0.63
td	202	419	424	482	471.7
R^2	0.99	0.99	0.99	0.99	0.99

Table V: The value of diffusional exponent n and correlation coefficients.

Formula	1	2	3	4	5
n	0.65	0.58	0.47	0.51	0.58
R^2	0.994	0.997	0.999	0.998	0.999

The Td of Weibull parameters calculated from the linear part of the dissolution curves (10-80%) and their correlation coefficients presented in Table IV shows excellent correlations for all formulations suggesting this model solid. As expected, a significant difference was noticed between Td values of the two matrixes. The lowest value was obtained with tablets containing only HPC. The partial T or total replacement of HPC by

Compritol 888 ATO® resulted in the increase of Td values. It can be assumed that the high values of Td obtained with differing proportions of the Compritol 888 ATO® can be attributed by its hydrophobic properties

Table V presents diffusional exponents n and their correlation coefficients computed by the least square method. The n values ranged from 0.47 to 0.68 for all formulations and indicated that a matrix diffusion controlled mechanism was operative[4]. When HPC was used alone as the tablet matrix n of 0.68 indicated non fickian diffusion, while in the case of Compritol alone, n was close to 0.5 thus indicating that the drug release followed fickian diffusion. In the case of various mixtures of both matrixes, the n values ranged from 0.47 to 0.58 and followed the same mechanism (fickian diffusion) as that observed with only Compritol. So, it appears that the effect of Compritol 888 ATO® inhibits that of the HPC and may be mainly responsible for the drug release regardless of its concentration in the formulation. These findings support the use of Compritol 888 ATO ® in the development of sustained release formula.

Conclusion

Weibull, Higuchi and Peppas models describe the kinetics of theophylline release from either Compritol or HPC matrixes. The drug released from the tablets containing Compritol 888 ATO® matrix followed fickian diffusion while the drug release from the tablets containing hydroxypropylcellulose matrix followed non-fickian diffusion. The results obtained indicated that the use of the Compritol 888 ATO® as a matrix agent makes possible the manufacture of tablets with the best mechanical properties and drug delivery system.

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