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PREPARATION OF ACETAMINOPHEN MICROCAPSULES BY COASERVATION-PHASE SEPARATION METHOD*

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ABSTRACT

In this study, it was aimed to prepare prolonged action microcapsules of acetaminophen with short biological half-life by a non-solvent addition method which is one of the coaservation-phase separation techniques.

For this purpose, the three different particle size ranges of acetaminophen (0.088 - 0.177 mm, 0.250 - 0.354 mm, 0.420 - 0.500 mm) were used. The solution of polyisobuthylene in cyclohexane as a non-solvent and Eudragit RS and Eudragit RL as coating polymers were also used. The prepared microsapsules were compressed by a hydraulic press using different types of direct tableting agents such as Ludipress, Avicel PH 101 and Lactose EP D 30. Dissolution rates of each tablet containing 160 mg of microencapsulated acetaminophen were examined by continuous flow-through cell method

The results of this study showed that the release rate of drug from microcapsules prepared with Eudragit RS was lower than that of microcapsules prepared with Eudragit RL. However different

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particle size ranges of drug didn't affect significantly the release rate; but different types of direct tableting agents were effective on the release rate of drug.

INTRODUCTION

Acetaminophen is a substance with short biological half-life ($t_{1/2}$ = 2-3 hours) and has bitter taste(1,2). These are two metabolites of acetaminophen in organism. One of these is conjugated form with glucuronic acide, and the other metabolite is hydroxylated form to active metabolite. This second metabolite is hepatotoxic at level of high concentration. To prevent this effect, it has been thought to decrease the absorption rate(3).

Therefore, in this study it was aimed to prepare prolonged action microcapsules of acetaminophen and so, to provide slow release of acetaminophen. For this purpose, non-solvent addition method which is one of the coacervation-phase separation techniques were used. As a coating materials Eudragit RS and Eudragit RL and three different particle size ranges of acetaminophen were used. the content uniformity and theoretical wall thickness values of prepared microcapsules were determined.

These microcapsules were tableted with different types of direct tableting agent at a constant pressure. Then, drug release rate and kinetics from tablet were examined. In addition, the effect of particle size of drug and structure of coating polymer were observed.

MATERIALS and METHODS

Materials:

Acetamiophen(Atabay Drug Comp.Türkiye), Eudragit RS 100 and Eudragit RL 100, cyclohexane (Roehm Pharma,GmbH,Darmstadt, Germany).Polyisobutylene,crosslinked polyvinylpyrrolidone(Kollidon CL) and Ludipress(BASF, Germany).Microcrystalline cellulose (Avicel PH 101, FMC Corp.USA). Directly compressible lactose (Lactose EP D 30, Meggle GmbH, Germany). Chloroform(BDH Ltd. England).

Table 1- Coding of prepared microcapsules.

Coating Polymer	Particle Size Ranges of Drug		
	0.088-0.177 mm	0.250-0.354 mm	0.420-0.500 mm
Eudragit RL	FL1	FL2	FL3
Eudragit RS	FS1	FS2	FS3

Methods:

I - Preparation of Microcapsules:

5 gr of crystalline acetaminophen of which particle size ranges determined formerly as (0.088-0.177 mm or 0.250-0.354 mm or 0.420-0.500 mm) was added to a three-nected flask containing 20 g chloroformic solution of 6 % w/w polyisobutylene(PIB)and coating polymer 8 % w/w (Eudragit RL or Eudragit RS). The "non-solvent" solution (60 g of PIB 6 % w/w in cyclohexane) was dropped into the flask at a constant rate of 0.9 g/ml thereby gradually reducing the solubility of the Eudragit. A constant stirring rate (300 rpm) was provided by using a magnet. Temperature (25° C) was maintained throughout the production.

Two minutes after the formation process was completed, the microcapsules precipitated and were separated by decantation and rinsed twice with 100 ml portions of cyclohexane to remove any PIB adsorbed at the microcapsule interface and empty wall polymer droplets. By means of an additional 50 ml of cyclohexane, they were transferred, vacuum filtered and solvent traces finally removed on paper at room temperature(4)(Table 1).

II- Evaluation of the Prepared Microcapsules:

II.1.1- Determination of Drug Content:

The samples containing theoretically 160 mg of acetaminophen were taken from the three different points of obtained microcapsules bulk. Thesesamples were dissolved in methanol and assayed spectrophotometrically for acetaminophen at 246.5 nm using a calibration curve

Table 2- Theoretical wall thickness and core material content of prepared microcapsules.

Code of microcapsule	Core material content (% w/w)	Wall thickness Theor. (μm)
FL1	73.0	7.68
FS1	72.6	7.83
FL2	77.4	14.2
FS2	75.3	15.7
FL3	73.2	26.1
FS3	74.4	25.1

based on standart solutions in methanol. This determination was repeated for three times (Table 2).

II.1.2- Determination of Theoretical Wall Thickness:

The theoretical wall thickness of microcapsules were calculated from the particle size of core material(r_1), the relative densities of the core and wall material(dc,dw)and the drug content in the microcapsules(F)using the following equation(5,6)(Table 2).

$$r_2 - r_1 = \left[\left(\frac{dc}{dw} \left(\frac{1}{F} - 1 \right) + 1 \right)^{1/3} - 1 \right] r_1$$

II.1.3- Determination of Density:

The densities of drug and coating polymers were determined picnometrically. As dispertion mediums, petroleum ether for the drug and liquid vaseline for Eudragit RL/RS were used. The densities were; acetaminophen 1.231 g/ml, Eudragit, 1.176 g/ml.

II.2- Selection of Excipients to be Used in Tablet Compression and Preparation of Tablets:

The prepared microcapsules were compressed in the form of tablets that contain 160 mg of acetaminophen. For this purpose, the

Table 3- Direct tableting agents used for preparation of microcapsule tablets.

Direct Tableting Agents(DTA)	Coding
Ludipress	YL
Avicel PH 101	YA
Lactose EP D 30	YE
Lactose EP D 30 + Kollidon CL (99.5 + 0.5)	YE1
Lactose EP D 30 + Ac-Di-Sol (99 + 1)	YE2
Lactose EP D 30 + Ac-Di-Sol (97 + 3)	YE3

different types of direct tableting agents(DTA)were used (Table 3). But a süper disintegration agent with wicking action was added to Lactose EP D 30 to compare with Ludipress containing 3.4 % of Kollidon(7). The tablets were prepared with each of excipients shown in Table 3 using same type of microcapsules at the constant pressures. Than dissolution tests of these tablets were made and drug release profiles were drawn(Fig.1). The type of DTA to be used in the tablet formulations has been determined from the examination of the release profiles.

The drug contents of microcapsules obtained after every production process were determined and the amount of microcapsules corresponding to 160 mg of acetaminophen was calculated. Then the calculated amount of microcapsules were mixed separetely with each of selected three excipients such as Ludipress, Avicel PH 101, Lactose EP D 30 + Kollidon CL . This mixture was pressed by hydraulic press at a pressure of 111.96 MPa. During the compression, the pressure was maintained 15 sec. The punch of 10 mm diameter was used(8).

The tablet formulations consisting of the microcapsules (Table 1) and excipients are shown in Table 4.

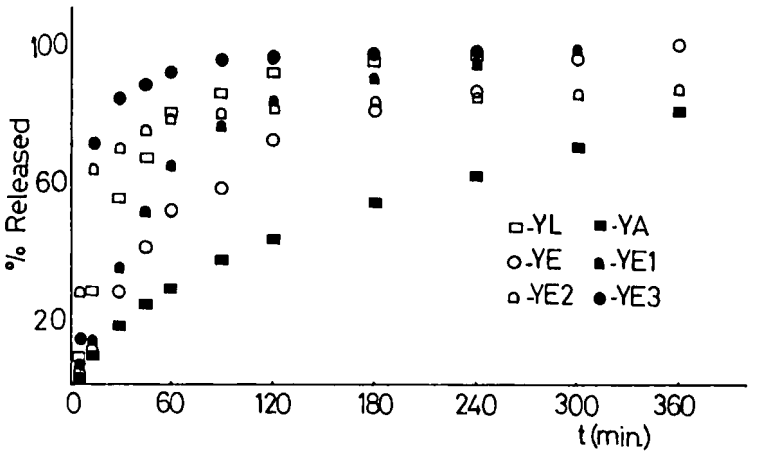


FIGURE 1
Profiles of dissolution rate of microcapsules pressed by using direct tableting agents shown in Table 3.

II.3- Dissolution Rate:

Drug release from the pressed microcapsules was assesed using flow through cell(Column method,Desaga). pH 5.8 phosphate buffer was used as dissolution medium. Flow rate was 2 ml/min. The samples were taken at intervals of 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, 420 minutes and assayed spectrophotometrically for acetaminophen at 240.5 nm using a calibration curve based on standart solutions in pH 5.8 phosphate buffer. The test was repeated for four times. The release rate profiles were drawn as the percent of cumulative amount of drug versus time.

RESULTS and DISCUSSION

The release profiles of drug from microcapsules pressed with different types of DTA's were shown in Fig 2(a,b,c,d,e,f).Generally, The drug release rate from formulations prepared with microcapsules decreased when were compared to the formulations prepared with crystalline acetaminophen (FKA, FKB, FKC). Also, the drug release

Table 4- Coding of microcapsules pressed by using direct tableting agents.

Formula	FL1A	FL1B	FL1C	FL2A	FL2B	FL2C	FL3A	FL3B	FL3C	FS1A	FS1B	FS1C	FS2A	FS2B	FS3C	FS3A	FS3B	FS3C
	mg																	
FL1	219	219	219															
FL2				206	206	206												
FL3							217	217	217									
FS1										220	220	220						
FS2													212	212	212			
FS3																215	215	215
Ludipress	200			200			200			200			200			200		
Avicel PH 101		200			200			200			200			200			200	
Lactose EP D 30			188			188			188			188			188			188
Kollidon CL			2			2			2			2			2			2

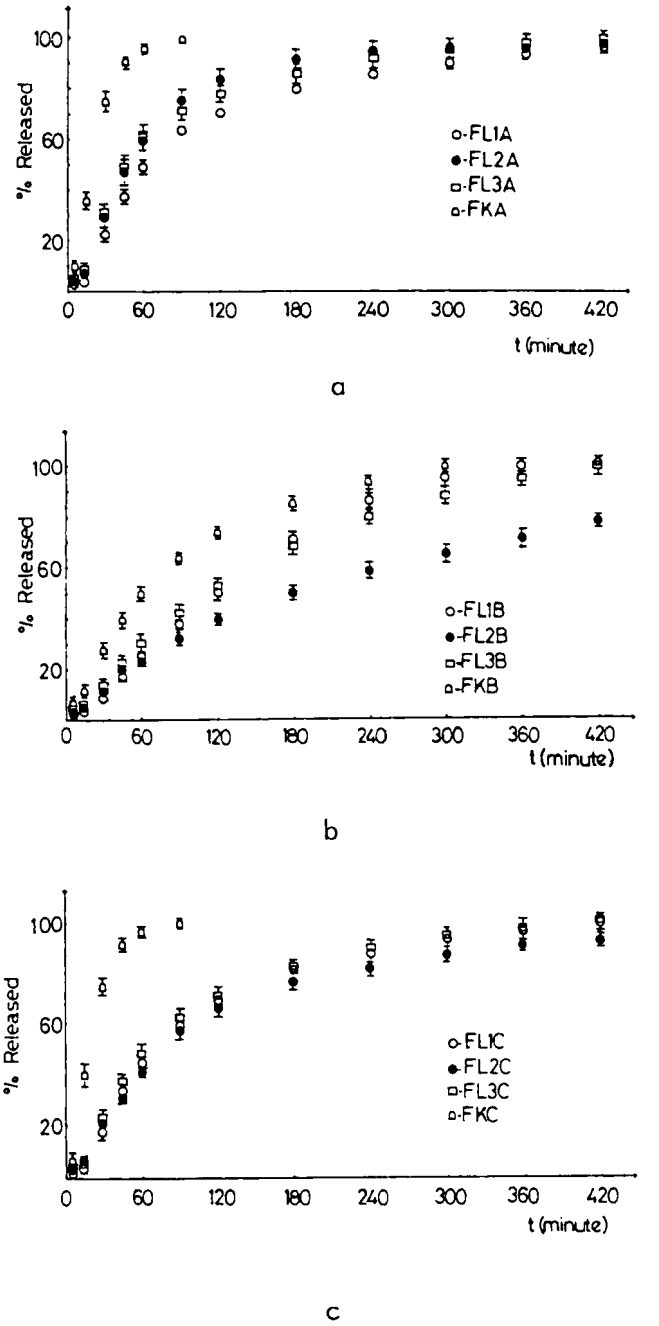
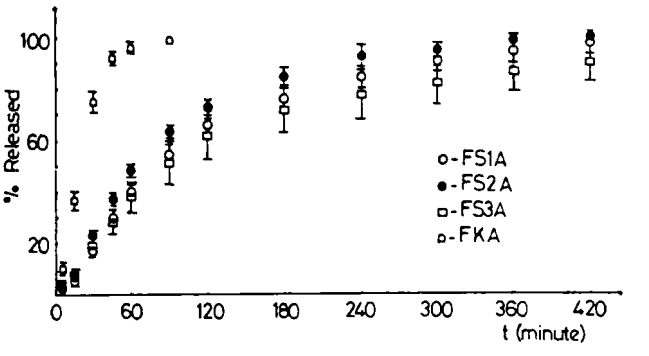


FIGURE 2 (a,b,c).

In vitro dissolution profiles of formulations.

FKA: Uncoated drug pressed by using Ludipress.
FKB: Uncoated drug pressed by using Avicel PH 101.
FKC: Uncoated drug pressed by using Lactose EP D 30 and Kollidon CL.



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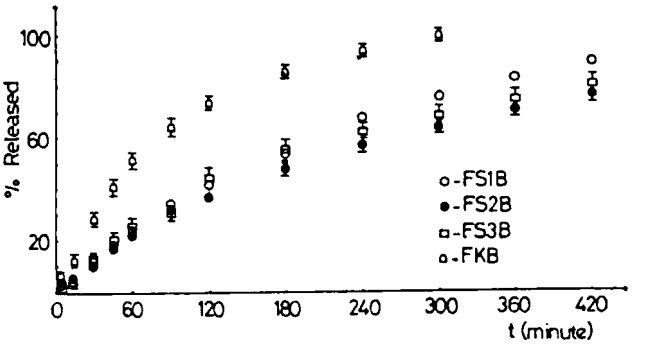

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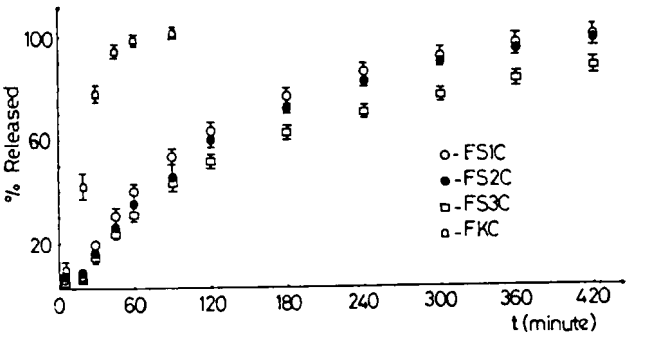

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FIGURE 2 (d,e,f)

In vitro dissolution profiles of formulations.

FKA: Uncoated drug pressed by using Ludipress.
FKB: Uncoated drug pressed by using Avicel PH 101.
FKC: Uncoated drug pressed by using Lactose EP D30 and Kollidon CL.

Table 5- Kinetic parameters.

Applied kinetics		Formula					
		FL1A	FL1B	FL1C	FS1A	FS1B	FS1C
Zero order	k_r^o	0.2302	0.2663	0.2403	0.2371	0.2202	0.2382
	r^2	0.7888	0.9285	0.8161	0.8516	0.9558	0.8665
First order	$k_r \times 10^{-3}$	7.837	9.045	7.731	7.827	8.294	7.766
	r^2	0.4595	0.6044	0.5041	0.5243	0.6147	0.5533
Higuchi	k_H	9.154	9.998	8.481	9.247	8.258	9.310
	r^2	0.9261	0.9887	0.9425	0.9623	0.9971	0.9726
Modified Hixson-Crowell	a	1.249	1.362	1.253	1.192	1.151	1.280
	$b \times 10^{-3}$	2.763	2.578	2.858	2.422	1.622	2.986
	r^2	0.9301	0.9935	0.9579	0.9620	0.9835	0.9697

Table 6- Kinetic parameters.

Applied kinetics		Formula					
		FL2A	FL2B	FL2C	FS2A	FS2B	FS2C
Zero order	k_r^o	0.2229	0.1842	0.2220	0.2376	0.1848	0.2416
	r^2	0.6797	0.9330	0.8121	0.7942	0.9470	0.9018
First order	$k_r \times 10^{-3}$	7.193	7.846	7.184	7.306	8.120	8.151
	r^2	0.4207	0.5691	0.5091	0.4825	0.5947	0.5511
Higuchi	k_H	9.171	9.961	8.769	9.436	6.027	9.214
	r^2	0.8506	0.9963	0.9412	0.9307	0.9978	0.9795
Modified Hixson-Crowell	a	1.220	1.126	1.137	1.184	1.108	1.212
	$b \times 10^{-3}$	3.235	1.380	2.305	2.874	1.286	2.330
	r^2	0.9038	0.9536	0.9399	0.9582	0.9715	0.9609

Table 7- Kinetic parameters.

Applied kinetics		Formula					
		FL3A	FL3B	FL3C	FS3A	FS3B	FS3C
Zero order	k_r^o	0.2235	0.2445	0.2380	0.2159	0.1962	0.2068
	r^2	0.7802	0.9278	0.8056	0.8340	0.9269	0.9059
First order	$k_r \times 10^{-3}$	6.722	8.164	7.174	7.798	8.483	7.501
	r^2	0.4338	0.5828	0.5009	0.5103	0.5701	0.5735
Higuchi	k_H	9.097	9.303	9.710	8.469	7.439	7.919
	r^2	0.8824	0.9929	0.9376	0.9526	0.9923	0.9866
Modified Hixson-Crowell	a	1.162	1.194	1.178	1.175	1.206	1.088
	$b \times 10^{-3}$	3.175	2.169	1.828	1.119	1.589	1.600
	r^2	0.9318	0.9829	0.9628	0.9447	0.9589	0.9702

rate from formulations coated with Eudragit RS was lower than that of formulations coated with Eudragit RL. Because, Eudragit RS contain little number of quaterner ammonium groups and consequently its hydrophilicity is low (9).

If amount of coated polymers is kept constant, the wall thickness of microcapsules increase as the particle size of drug increase, because, surface area of the particles decrease(10,11). This situation shown in Table 2, cause slow relase of drug in application. But, the microcapsule wall get damaged during the tableting process because of applied pressure. Sothe drug release from microcapsules modified into drug release from porous matrix. Therefore, the effects of particle sizeof drug and wall thickness of individual microcapsules on the drug release were not very important.

In addition, the drug release from tablets also depended on types of DTA's used in tablet formulations. In all formulations, the drug release from tablets pressed with Avicel PH 101 was slow, because a disintegrating agent was not used in these tablet formulation. But, the other formulations included different ratios of Kollidon CL as a disintegrating agent; Ludipress which was used in formulations, contains structurally 3.4 % Kollidon CL. Also, 0.5 % Kollidon CL was added to the formulations prepared with Lactose EP D 30.

The results obtained from dissolution tests were applied to four different kinetics such as zero order, first order, Higuchi, modified Hixson-Crowell. The best harmony was obtained for Higuchi kinetic model, modified Hixson-Crowell, zero order and first order kinetics in the written order (Table 5, 6, 7).

Especially, the drug release from all of formulations which were with Avicel PH 101, fitted Higuchi model (12). This harmony decreased in the formulations containing Kollidon CL as shown Fig.3. But it was observed that the main model described to obtain best harmony with drug release kinetic from tablets of microcapsules was Higuchi model. This result was identical to that of ethyl cellulose walled microcapsules studied by Jalsenjak (13,14)and Alpan et.al.(15).

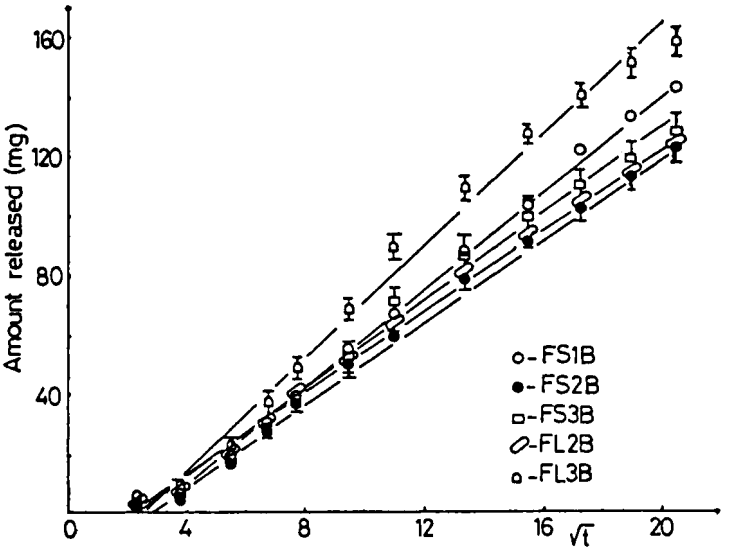

FIGURE 3

Dissolution profiles according to Higuchi kinetic.

The results of this study showed that acetaminophen is microcapsulated according to our purpose by the non-solvent addition method.

But the necessary ,

* To optimize mixing efficiency based on geometry of coaservation container and on chosen particle size range, and to realize validation parameters according to these conditions.
* To increase the wall thickness of microcapsules for slow drug release.
* To select suitable DTS's which were utilized for compression of microcapsules.

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REFERENCES

1 - Australian National Drug Information Service, Austr.J.Pharm., Nov., 857 (1984).

2 - J.Rak, M.Chalabala, V.Walters, Acta Fac.Pharm.Univ.Cameniance, Tom.XXXV,7 (1980).

3 - K.Duckova, M.Chalabala, J.Baluch, J.Rak, Acta Fac.Pharm.Univ. Comenianae, Tom.XXXVIIII, 5 (1984).

4 - S.Benita, A.Hoffman, A.Donbrow, J.Pharm.Pharmacol.,37, 391 (1985).

5 - S.Benita, Labo Pharma Probl.Tech., 32, 697 (1984).

6 - J.A.Herbig, "Microencapsulation" Encyclopedia of Chemical Technology, 2nd ed., Vol.13, Willey & Sons Inc., New-York, p.436, 1967.

7 - T.Baykara, G.Duman, K.Ş.Özşener, Ş.Ordu, B.Özateş, Drug Dev. Ind.Pharm.,17(17), (1991)(in press).

8 - K.Marshall, Drug Dev.Ind.Pharm., 15(13), 2153 (1989).

9 - R.K.Chang, C.Hsiao, Drug Dev.Ind.Pharm., 15, 187 (1989).

10- Y.Kawashima, S.Y.Lin, S.Kasai, H.Takenaka, K.Matsunami, Y.Nochida, H.Hirose, Drug Dev.Ind.Pharm., 10, 467 (1984).

11- R.Ruiz, A.Sakr, O.L.Sprockel, Drug Dev.Ind.Pharm., 16(11), 1829 (1990).

12- T.Higuchi, J.Pharm.Sci., 52,1145 (1963).

13- I.Jalsenjak, C.F.Nicolaidou, J.R.Nixon, J.Pharm.Pharmacol., 28, 912 (1976).

14- I.Jalsenjak, J.R.Nixon, R.Senjkovic, I.Stivic, J.Pharm. Pharmacol., 32, 678 (1980).

15- H.Oya Alpar, V.Walters, J.Pharm.Pharmacol., 33 , 419 (1981).