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COMMUNICATION

Development and In Vitro Evaluation of a Buccoadhesive Pindolol Tablet Formulation

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ABSTRACT

Controlled-release buccoadhesive tablets containing pindolol were prepared and evaluated in order to achieve constant plasma concentrations during the treatment of chronic hypertension and to improve the bioavailability of pindolol by the avoidance of hepatic first-pass metabolism. The formulations were tested for weight, hardness, friability, content uniformity, swelling rate, bioadhesive force, and drug release rate values. Carbopol 934 and NaCMC were used as bioadhesive polymers and Methocel K4M, Methocel K15M, and HPC were added as matrix-forming polymers.

MATERIALS

Pindolol (Sandoz, Switzerland), hydroxypropylmethylcellulose (Methocel K4M, Methocel K15M) (Colorcon, England), hydroxypropylcellulose (HPC), (Aqualon, Wilmington, DE), and Carbopol 934 (Briesfeld, Germany) were used. All other chemicals, either reagent or analytical grade, were used as received.

METHODS

Solubility Measurement of Pindolol

Pindolol in an amount in excess of its solubility was dispersed in 50 ml of dissolution media in a 100-ml stoppered bottle and shaken in a water bath at 37°C until saturation. One-milliliter samples were withdrawn, di-

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luted, and assayed spectrophotometrically at 287 nm (Varian 634, Palo Alto, CA). Solubilities in pH 6.8 phosphate buffer solution and in pH 6.8 phosphate buffer solution:methanol (98:2) mixture were determined. Calibration curves were used for the determination of the amounts dissolved. Mean values of three tests are given.

Buccoadhesive Tablet Formulation and Preparation

Pindolol was mixed manually in glass bottles with different ratios of Methocel K4M, Methocel K15M, HPC, Carbopol 934, and NaCMC for 30 min and then compressed into tablets weighing 100 mg by using a flat-faced punch of 8.5 mm diameter (tablet press, Aymes, Turkey). The composition of the buccoadhesive tablet formulations are shown in Table 1.

Tablet Content Uniformity

One tablet was powdered, treated with enough pH 6.8 phosphate buffer solution:methanol mixture (98:2) to make 50 ml, diluted, and analyzed spectrophotometrically at 287 nm. Five tablets of each formulation were assayed.

Tablet Weight Variation

For each formulation 20 tablets were examined.

Tablet Hardness

For each formulation 10 tablets were examined using a Schleunger hardness tester (Switzerland).

Tablet Friability

For each formulation 10 tablets were tested using a Roche-type friabilitor.

In Vitro Swelling Rate Studies

For each formulation three tablets were tested. After the weight, diameter, and height were determined, the tablet samples were immersed in pH 6.8 phosphate buffer solution maintained at 37°C. After 1 hr the tablets were removed and weight, diameter, and height were measured. The normalized swollen value/initial value ratios were calculated (1).

In Vitro Bioadhesion Studies

The bioadhesive forces of the tablets were measured using a tensile tester apparatus (Tensilon UTM II, Toyo Measuring Instruments Co. Ltd., Japan) and bovine buccal mucosa (2). Fresh bovine buccal mucosa obtained at slaughter were rapidly frozen to -30°C. Before use a 2-mm-thick section of mucosa was cut and brought to room temperature in 0.9% sodium chloride solution. A tablet was attached to the upper clamp and buccal mucosa section was attached to the lower clamp using a liquid cyanoacrylate adhesive. pH 6.8 phosphate buffer solution (10 μl) was placed on the tablet surface using a Hamilton syringe and the two surfaces were brought into contact with a force of 44 g. After 10 min the tablet–mucosa system was attached to the tensile tester apparatus and stretched at constant speed. The maximum detachment force was recorded. The reported data are the means of three determinations.

In Vitro Release Studies

The dissolution rates of pure drug and the buccal tablets were studied using the USP XXII rotating basket method under sink conditions at 37 ± 0.5°C and 50 rpm (Modal Technik AG-4000, Switzerland). Samples of pure drug weighing 100 mg and tablets containing 10 mg pindolol were added to 500 ml of pH 6.8 phosphate buffer solution:methanol (98:2) mixture. Samples were withdrawn at certain time intervals and replaced with fresh dissolution medium. The amount of pindolol released was determined spectrophotometrically at 287 nm and the release rate data were evaluated kinetically. No interference of the ingredients was determined. The reported data are the means of three determinations.

RESULTS AND DISCUSSION

The equilibrium solubility of pure pindolol in phosphate buffer solution pH 6.8 and in the mixture of pH 6.8 phosphate buffer solution:methanol (98:2) were found to be 8.2 μg/ml and 222.2 μg/ml, respectively. The buffer solution:methanol mixture was chosen as dissolution medium to achieve sink conditions.

All of the tablets were acceptable in regard to pindolol content, weight variation, and friability. Tablets with crushing strengths between 2.6–11.2 kg were obtained with Carbopol 934, hardness decreasing with increasing amounts of HPMC and HPC. NaCMC alone was not directly compressible; the hardness of the tablets containing NaCMC was much lower, ranging from 1.5 to 3.4 kg and increasing with increasing amounts of HPMC and HPC. The differences in the tablet strengths are reported not to affect the release of the drug from

Table 1

Composition of the Buccoadhesive Tablet Formulations

Code	A	AI_{30}	AI_{60}	I_{90}	AII_{30}	AII_{60}	II_{90}	$AIII_{30}$	$AIII_{60}$	III_{90}	B	BI_{30}	BI_{60}	BII_{30}	BII_{60}	$BIII_{30}$	$BIII_{60}$
Pindolol	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Carbopol 934	90	60	30	—	60	30	-	60	30	—	—	—	—	—	—	—	—
NaCMC	—	—	—	—	—	—	—	—	—	—	90	60	30	60	30	60	30
HPMC K4M	—	30	60	90	—	—	—	—	—	—	—	30	60	—	—	—	—
HPMC K15M	—	—	—	—	30	60	90	—	—	—	—	—	—	30	60	—	—
HPC	—	—	—	—	—	—	—	30	60	90	—	—	—	—	—	30	60

hydrophilic matrices. Drug is released by diffusion through the gel layer and/or erosion of this layer and is therefore independent of the dry state of the tablet (3).

The swelling behavior of the tablets is important in regard of bioadhesion and drug release (4). No measurements could be done with 90% Carbopol 934 matrix and with the matrices containing HPC, because they lost their shapes at the end of the first hour. The normalized swelling values of the matrices with Carbopol 934 and HPMC increased with increasing amounts of Carbopol 934 ($p < 0.05$). Carbopol 934 is more hydrophilic than HPMC and if added in high ratios causes high release rates (5). Maximum swelling was seen with the formulations containing NaCMC and HPMC, the values increasing with increased amounts of NaCMC ($p < 0.05$). No difference was determined between the swelling values of the matrices containing Methocel K4M and Methocel K15m ($p < 0.05$) (Table 2).

The bioadhesion characteristics were affected by the type and ratio of the bioadhesive polymer (Table 3). The highest detachment force was observed with the formulation A prepared with 90% Carbopol 934, this followed by AI_{30} and AII_{30} formulations. Increasing the content of Carbopol 934 resulted in increased detachment forces ($p < 0.05$), which is in compliance with the literature (6). The tablets of the formulations BI_{30} and BII_{30} containing NaCMC as bioadhesive polymer were laminated during the experiment, which might be caused by the low hardness of the tablets. The detachment forces of BI_{60} and BII_{60} were found to be lower than those of AI_{60} and AII_{60} ($p < 0.05$). The differences between Methocel K4M and K15M were not significant ($p < 0.05$), whereas HPC results showed low values ($p < 0.05$). This is because HPMC has bioadhesive properties contrary to HPC (7). The results indicate that the bioadhesion of Carbopol 934 is stronger than NaCMC (8).

Table 2

Normalized Swelling Values of the Buccoadhesive Tablet Formulations

Code	$p \pm$ SD (g/g)	$q \pm$ SD (mm^3/mm^3)
AI_{30}	5.37 ± 0.16	5.23 ± 0.13
AI_{60}	4.06 ± 0.12	3.98 ± 0.90
I_{90}	3.62 ± 0.04	3.36 ± 0.22
AII_{30}	5.04 ± 0.04	5.46 ± 0.03
AII_{60}	4.64 ± 0.36	3.86 ± 0.25
II_{90}	3.60 ± 0.15	3.46 ± 0.24
BI_{30}	8.03 ± 0.15	8.57 ± 0.41
BI_{60}	6.10 ± 0.18	6.14 ± 0.09
BII_{30}	7.99 ± 0.18	8.21 ± 0.30
BII_{60}	6.09 ± 0.51	5.85 ± 0.33

Table 3

Detachment Force Between Buccoadhesive Tablets and Buccal Mucosa

Code	Detachment Force (kPa)
A	64.0 ± 1.0
AI_{30}	35.7 ± 2.2
AI_{60}	23.0 ± 3.2
I_{90}	7.1 ± 0.4
AII_{30}	29.8 ± 1.2
AII_{60}	24.1 ± 2.2
II_{90}	9.1 ± 1.0
$AIII_{30}$	18.0 ± 2.5
$AIII_{60}$	8.2 ± 2.1
III_{90}	3.4 ± 1.0
BI_{30}	-
BI_{60}	12.8 ± 1.4
BII_{30}	-
BII_{60}	7.3 ± 1.0
$BIII_{30}$	8.3 ± 2.0
$BIII_{60}$	6.9 ± 0.5

The release of pindolol from buccoadhesive tablets varied according to the type and ratio of the matrix-forming polymer used (Figs. 1, 2, and 3). The release rate of pindolol decreased with increasing concentrations of Methocel K4M and K15M in AI, AII and BI, BII formulations. On the whole, the viscosity of HPMC affects the release rates, but the difference between AI and AII was not significant ($p < 0.05$). Those formulations containing HPC as matrix-forming polymer did not show sufficient control of drug and released their whole pindolol content in a period of 4–6 hr. The type and ratio of the bioadhesive polymer also altered the release rate. Carbopol 934 is more hydrophilic than HPCM; it can swell rapidly, therefore decrease of Carbopol 934 content delays the drug release from A formulations (9). NaCMC can swell and erode rapidly, which explains the relatively high release rates of pindolol from B formulations (Table 2) (10).

To characterize the release mechanism of pindolol, the dissolution data ($M_t/M_\infty < 0.60$) were evaluated according to the equation (11):

$$M_t/M_\infty = kt^n$$

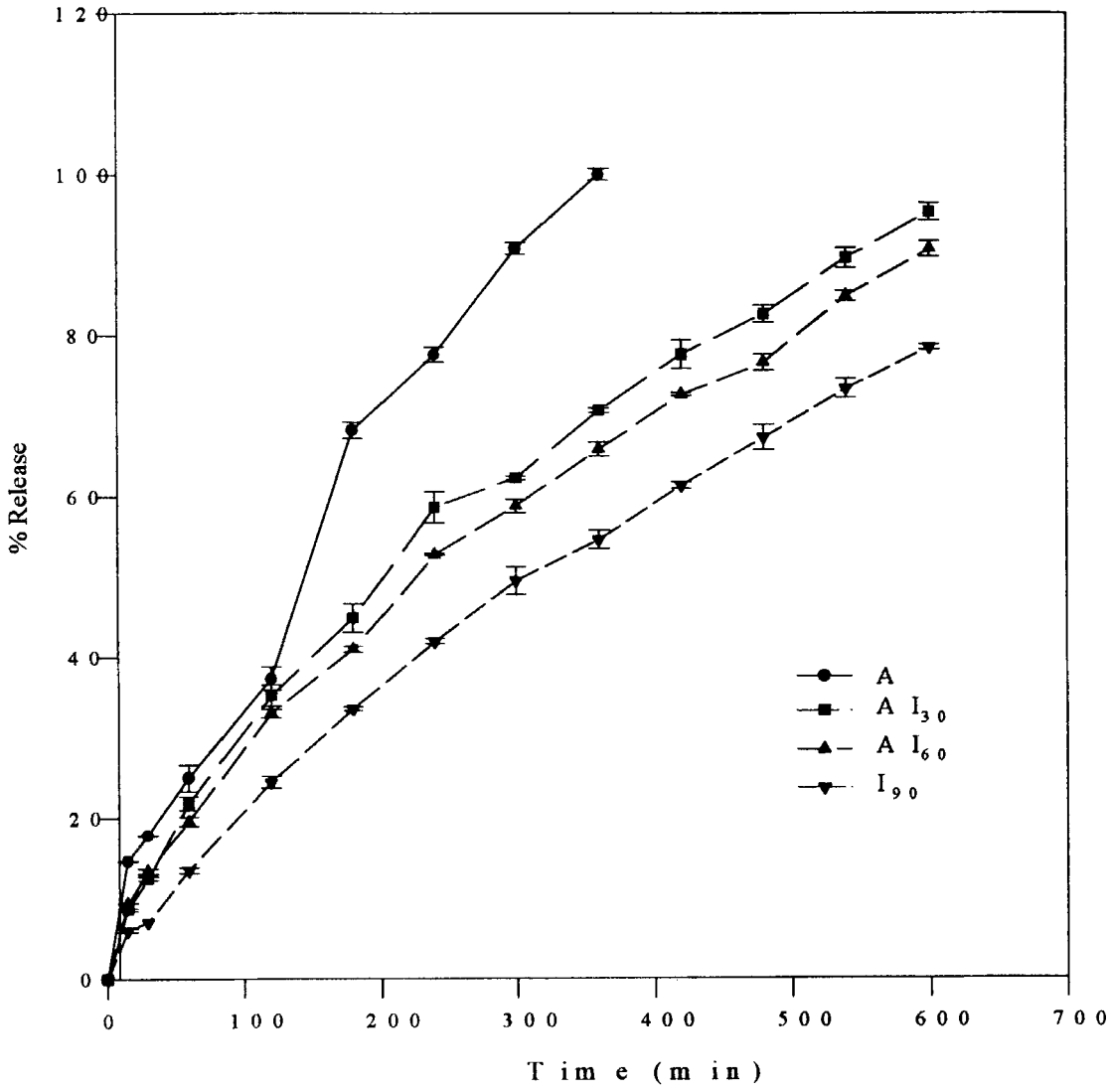

Figure 1. In vitro profiles of pindolol from buccoadhesive tablet formulations containing different ratios of Carbopol 934 and Methocel K4M.

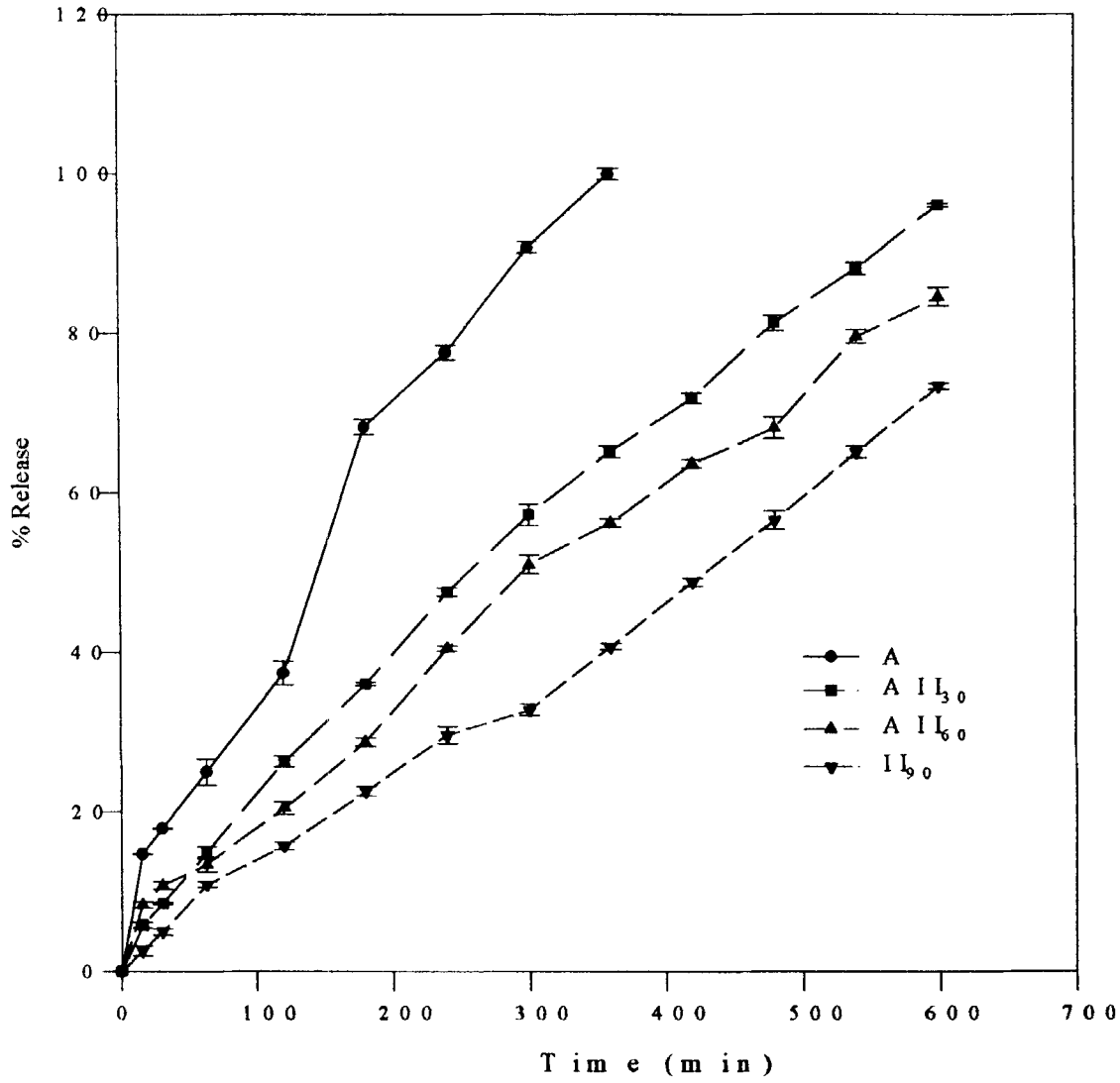

Figure 2. In vitro release profiles of pindolol from buccoadhesive tablet formulations containing different ratios of Carbopol 934 and Methocel K15M.

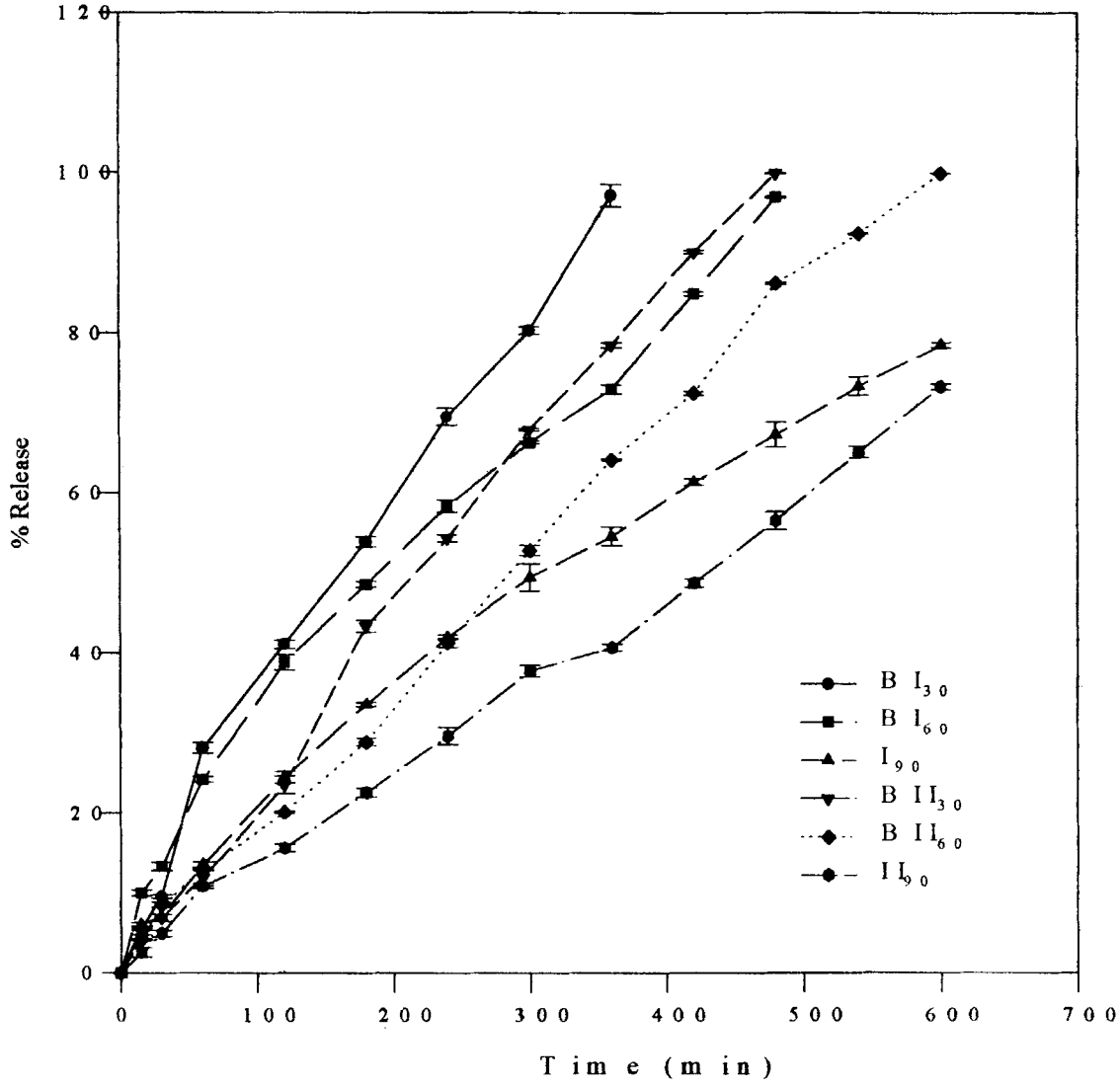

Figure 3. In vitro release profiles of pindolol from buccoadhesive tablet formulations containing different ratios of NaCMC and Methocel K4M or K15M.

Table 4

Estimated Values of k and n *by Regression of log* M_t/M_∞ *on log* t

Code	r^2	n	k
A	0.995	0.530	2.985
AI_{30}	0.996	0.695	1.263
AI_{60}	0.804	0.681	1.096
I_{90}	0.997	0.740	0.716
AII_{30}	0.999	0.846	0.454
AII_{60}	0.991	0.930	0.237
II_{90}	0.983	0.981	0.187
$AIII_{30}$	0.998	0.953	0.497
$AIII_{60}$	0.971	0.896	0.579
III_{90}	0.998	0.602	2.340
BI_{30}	0.998	0.602	2.340
BI_{60}	0.997	0.640	1.748
BII_{30}	0.981	0.923	0.319
BII_{60}	0.984	0.925	0.216
$BIII_{30}$	0.969	0.941	0.392
$BIII_{60}$	0.935	0.890	0.531

Table 5

Kinetic Assessment of Release Data (r^2)

Code	Zero-Order	$\sqrt{t}$
A	0.977	0.988
AI_{30}	0.969	0.997
AI_{60}	0.979	0.995
I_{90}	0.985	0.993
AII_{30}	0.993	0.986
AII_{60}	0.994	0.966
II_{90}	0.995	0.947
$AIII_{30}$	0.999	0.977
$AIII_{60}$	0.989	0.935
III_{90}	0.998	0.934
BI_{30}	0.985	0.988
BI_{60}	0.985	0.989
BII_{30}	0.995	0.972
BII_{60}	0.997	0.957
$BIII_{30}$	0.973	0.956
$BIII_{60}$	0.977	0.971

The values found for n are between 0.5 and 1 in all cases exhibiting a non-Fickian release behavior controlled by a combination of diffusion and chain relaxation mechanism (Table 4). Different kinetic equations were applied to interpret the release rate from the matrices. The results of the formulations containing Methocel K4M best fitted square root of t kinetics, whereas the data of all the other formulations best fitted zero-order kinetics (Table 5).

CONCLUSIONS

Regarding all of the properties evaluated, AI_{30} and AII_{30} formulations were found to be the best formulations to achieve the aim of this study. These matrices had good bioadhesive properties and released 95–96% of their pindolol content over a period of 10 hr.

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