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Development of a multiple-unit system: Tablets containing amlodipine besylate which have different release kinetics

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ABSTRACT: Multiple-unit systems may include tablets, capsules, pellets in a single administration. Once-a-day administration of Amlodipine Besylate (AML) accounts for fluctuation of plasma drug concentrations between dosing intervals. The aim of this study is to develop an extended-release (ER) and an immediate-release (IR) tablet to overcome the fluctuation of plasma drug concentrations. To achieve this purpose, 9 IR tablets and 6 ER tablet formulations were developed. The dissolution media for IR tablets was pH 2 for 1 hour and the dissolution media for ER tablets was pH 2 for 2 hours, and afterwards was pH 6.8 for 10 hours. The amount of AML released into the dissolution media was measured by Mettler Toledo UV 5 at a wavelength of 238 nm. The dissolution data of IR and ER tablets were statically evaluated. The highest dissolution rate for IR tablets (93%) was achieved with the IR-5 formulation. For ER tablets, a 50% drug release was achieved with the ER-1 and ER-4 formulation. The drug release kinetics of all ER tablets were calculated and subsequently the ER-1 formulation, which has Higuchi drug release kinetics, was chosen as the ER tablet. Lastly, a dissolution study of the selected formulations (IR-5 and ER-1) was conducted in the same vessel. After 12 hours of the dissolution study, drug release was found to be 79% ±0,92 (close to 75% which was targeted). Multiple-unit systems that have different tablet formulations in one administration could be used to enhance drug release kinetics that cannot be achieved with conventional tablets.

KEYWORDS: Multiple unit system; amlodipine besylate; immediate release tablet; extended release tablet; fluctuation of plasma drug concentration; hydroxyl propyl cellulose; sodium starch glycolate; crospovidon.

1. INTRODUCTION

The multiple-unit system is an approach which involves different dosage forms of drugs that have versatile release kinetics [1]. This approach enables the combination of delayed, extended and immediate release systems in one administration. Pharmacokinetic properties of drugs can be improved by designing the formulations of the drugs. Multiple-unit systems could comprise both the same and different dosage forms. Also, examples of multiple-unit systems could comprise one or more drugs. For instance, tablets and pellets could be placed in one capsule. Combining drugs that are in different dosage forms within the same application enhances patient compliance and gives a chance for better stability.

Tablets are the most preferred dosage form that are often used in the pharmaceutical market. Furthermore, immediate-release tablets may have the capability of disintegrating rapidly. Tablets that have the capability to disintegrate in the oral cavity without the need for water are referred to as "orally disintegrating tablets" (ODTs) [2]. Rapid disintegration may be achieved with high porosity. Thus, highly porous tablets can be manufactured using a freeze-drying (lyophilization) method [3]. A major problem for tablets manufactured by lyophilization is low hardness and high friability [4]. Issues of low hardness and high friability can be overcome by formulating conventional tablets. Further hardness can be achieved by using high pressure in conventional tablet production. Also, conventional tablets can be produced with more cost-efficient and simple methods. The direct compression method is one of the most well-known production methods that has fewer process steps. When this method is used in the production of tablets, high disintegrating ability is achieved with superdisintegrant materials. Frequently used superdisintegrants include sodium starch glycolate, crospovidone, croscarmellose, etc. [5, 6]. Superdisintegrants also have different mechanisms of action to disintegrate tablets. The main disintegration

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mechanisms of superdisintegrants are swelling, wicking, heat of wetting, chemical reaction (acid-base reaction), particle repulsive forces, deformation recovery, and enzymatic reaction [7, 8].

Extended-release tablets are used to balance plasma drug concentrations and to enable longer drug administration intervals. Extended-release, or controlled-release tablets, are manufactured to release the drug in a predetermined pattern over a certain period of time [9]. Extended-release kinetics of the drug in a tablet is achieved by the addition of excipients. These excipients slow down the drug release by forming a barrier, a diffusion Wall, between the drug and dissolution medium. Hydroxypropyl cellulose is one of the most preferred excipients that alters the drug release rate due to its molecular weight.

Hypertension is a major healthcare problem worldwide [10]. Calcium channel blockers help to reduce blood pressure by lowering the calcium flow into cells [11]. Amlodipine besylate (AML) is an oral dihydropyridine drug refers to as calcium channel blockers [12]. The peak plasma concentration (C_{max}) of AML is 6 to 9 hours after oral administration with daily doses of 2.5, 5, and 10 mg. Moreover, AML has a long terminal elimination time (40-50 hours) [13]. Once-a-day dosing causes a 20-25% fluctuation in plasma drug concentrations between dosing intervals. Additionally, following initiation of treatment with AML, steady-state plasma drug concentrations are achieved in 1 to 1.5 weeks [14].

The aim of this study was to develop a multiple-unit drug delivery system to overcome the fluctuation in plasma drug concentrations between dosing intervals of AML. It was thought that the simultaneous administration of an immediate-release tablet and an extended-release tablet could overcome this fluctuation. All tablets contained 6.944 mg of AML (equivalent to 5 mg Amlodipine). We developed nine formulations for immediate-release tablets and six formulations for extended-release tablets. The dissolution rate results of all IR formulations were compared at 5 minutes of the process. The fastest dissolution profile was achieved with formulation IR-5. For this reason, IR-5 was determined as the optimum formulation among the IR tablets. Drug release kinetics were calculated using the dissolution data of extended-release tablets. The 50% release of AML content within 12 hours was determined as the target for extended-release tablets. Afterwards, a dissolution study was conducted on the chosen formulations of IR and ER tablets.

2. RESULTS AND DISCUSSION

2.1. Characterization of tablets

All immediate-release and extended-release tablet formulations are shown in Table 3 and Tablet 4, respectively.

Weight variations, hardness, friability values, and disintegration times (DT) of immediate-release tablets are shown in Table 1. Tablet weight variations, hardness, and friability values of extended-release tablets are shown in Table 2.

Increased Kollidon CL amounts in the IR-1, 2, and 3 formulations increased the disintegration time (Table 1). No consistent correlation was found between the increasing amount of Primojel and decrease in the disintegration time (IR-1, 4 and 5) (Table 1), but a different conclusion was reached by Battu, S.K., et al. [15]. Their results showed that there was a correlation between increased amounts of Primojel and reduced DTs of tablets. This finding was due to the fact that the formulations (IR 1, 4, and 5) compared in our study contained two superdisintegrants while the formulations compared in the study by Battu S.K., et al. contained only one superdisintegrant. Both studies provide information about the effects that one or two superdisintegrants in a formulation have on disintegration behaviour. In IR-7, Kollidon CL was used alone as a superdisintegrant which considerably reduced the disintegration time, however, this phenomenon was not achieved with the other formulations which contained Kollidon CL as a mixture as seen in Table 1. The addition of mannitol or microcrystalline cellulose alone prolonged the disintegration time compared to their combined administration (IR-5, 8, and 9) (Table 1).

All IR formulations met pharmacopeial friability requirements (Table 1 and 2) (<1%) (European Pharmacopoeia 7.0) [16].

Due to insufficient powder properties, proper compression of some formulations could not be achieved, and their hardness values did not reach reasonable ranges (e.g. 6 – 8 kg) (Table 1).

In particular, the use of mannitol (IR-8) as a filler alone caused the tablet to become more brittle, and that led to a decrease in tablet hardness. Using microcrystalline cellulose (Avicel PH 102) alone (IR-9) offered better compatibility and tablet hardness than the addition of mannitol alone (Table 1).

Table 1. Tablet Control Results of IR tablets.

Formulation	Weight variation (mg)	Hardness (kg/cm²)	Friability (%)	Disintegration time (s)
IR-1	98.3±0.7	6.5±0.4	<1	16.6±1.5
IR-2	98.5±0.8	8±0.4	<1	25.6±2.4
IR-3	100.1±0.4	5.9±0.4	<1	23.7±1.9
IR-4	98.2±0.6	4.8±0.3	<1	31.5±1.6
IR-5	101±0.4	6.7±0.4	<1	18.1±1.4
IR-6	99.6±0.3	5.9±0.3	<1	54.4±1.4
IR-7	101.4±0.4	5.2±0.2	<1	8.04±1
IR-8	101.5±0.8	7.7±0.3	<1	37.1±3.5
IR-9	100.1±0.5	4.2±0.3	<1	26±2.3

Table 2. Tablet Control Results of ER tablets

Formulation	Weight variation (mg)	Hardness (kg/cm²)	Friability (%)
ER-1	98.8±1	9.6±0.8	<1
ER-2	99.8±0.6	8.7±0.2	<1
ER-3	99.8±0.5	8.9±0.3	<1
ER-4	99.1±0.9	8.47±0.4	<1
ER--5	99.6±0.5	9.7±0.7	<1
ER-6	99.2±0.5	10.6±0.5	<1

2.2. Evaluation of dissolution studies of IR and ER tablets

2.2.1. Evaluation of IR tablets

Dissolution plots of IR-1, 2, 3 and IR-1, 4 and 5 formulations using various quantities of different superdisintegrants are shown in Figure 1 and Figure 2, respectively. Since tablets IR-1 to IR-9 were immediate-release tablets, the dissolution data of the formulations at 5 minutes were compared with one-way ANOVA to determine the optimal formula. The dissolution data of all IR-formulations at 5 minutes were statistically significant ($p<0.05$). The IR-5 formulation, which gave the highest dissolution value at 5 minutes, was determined as the optimum formulation. The superdisintegrants in formulation IR-5 were used alone both in IR-6 and 7 to compare with the optimum formulation (IR-5) (Figure 3). In addition, two fillers in formulation IR-5 were used alone in separate formulations (IR-8 and 9) and were compared with IR-5 (Figure 4).

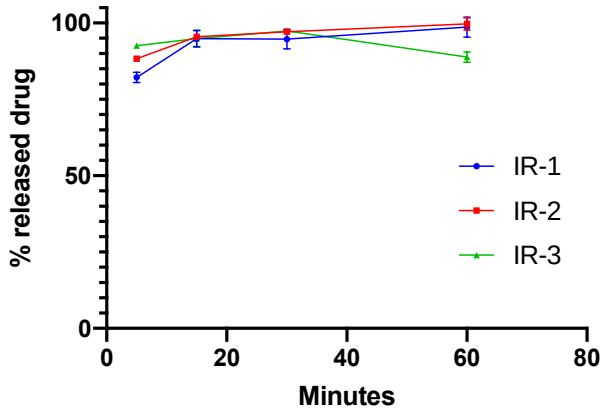


Figure 1. Comparison of the dissolution profiles of IR-1, 2, and 3 tablet formulations containing AML.

In dissolution studies of IR-1, 2, and 3 formulations, increasing the amount of crospovidone (Kollidon Cl) increased the percentage of dissolution at 5 minutes (Figure 1). On the other hand, increasing the amount of Primojel increased the percentage of dissolution at only 5 minutes, which was statistically significant ($p<0.05$) (Figure 2).

Dissolution results of IR-1, 4, and 5 showed that increasing the Primojel/tablet weight ratio affected the dissolution rate at 5 minutes. However, the differences in dissolution rate at 5 minutes were not statistically significant among all these formulations. The dissolution rate of IR-1 at 5 minutes was significantly different from IR-4 and IR 5 ($p<0.05$), but the dissolution rate between IR-4 and IR-5 was not statistically significant. The p-value of the post-hoc test was 0.056 ($p>0.05$).

The comparison of dissolution between IR-5, 6, and 7 formulations indicated that if tablets had two disintegrants (Primojel and Kollidon CL) instead of one superdisintegrant [17], the dissolution of the tablets increased and the differences at 5 and 15 minutes were statistically significant between these formulations ($p<0.05$) (Figure 3) [18, 19]. Raj, B.S. et al. found that the combination of Primojel and Kollidon CL as superdisintegrants, affected the dissolution rates of all formulations [21, 22], which correlates with our results.

In our study, an increased amount of Primojel affected dissolution rates more than Kollidon CL, however, previous studies by Jaya, S. et al. [20] found that Kollidon CL was more effective than Primojel (Figure 1, Figure 2).

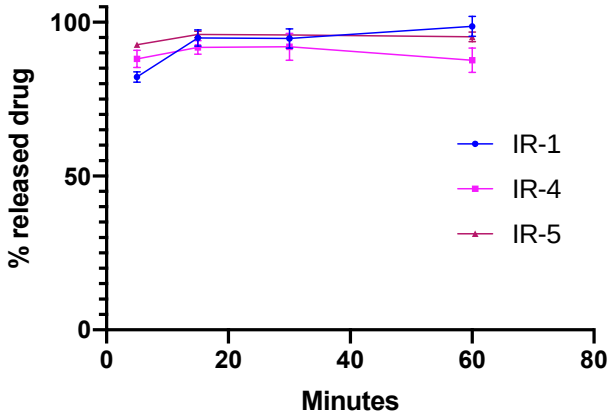


Figure 2. Comparison of the dissolution profiles of IR-1, 4, and 5 tablet formulations containing AML.

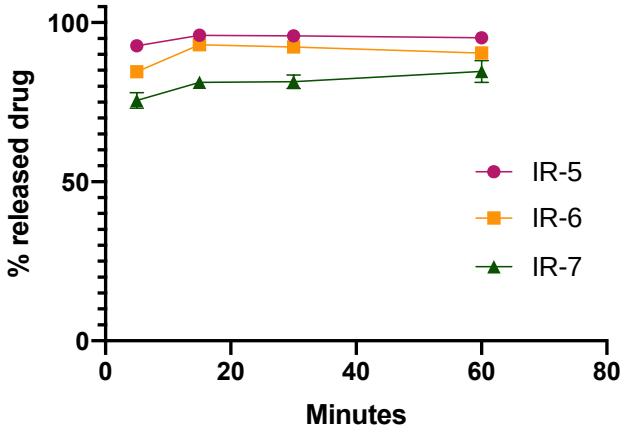


Figure 3. Comparison of the dissolution profiles of IR-5, 6, and 7 tablet formulations containing AML.

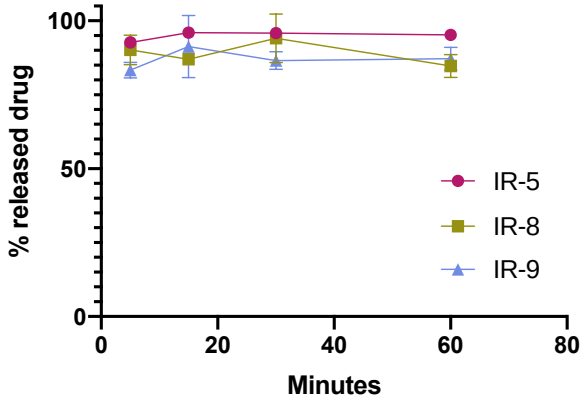


Figure 4. Comparison of the dissolution profiles of IR-5, 8, and 9 tablet containing AML.

2.2.2. Evaluation of ER tablets

Dissolution data of all ER formulations at 12 hours were compared with one-way ANOVA and the post-hoc Tukey test. A statistically significant difference was not found between only ER-1 and ER-4 formulations (p>0,05). ER-1 and ER-4 tablet formulations were selected as candidates, because both formulations released 50% of their drug content within 12 hours. In our study, we aimed to develop an ER tablet that could provide 50% drug release with zero-order kinetics in 12 hours. In this way, ER tablets could overcome the fluctuation of plasma drug concentrations between dosing intervals of AML. When the drug release kinetics of these formulations were compared, the ER-4 formulation conformed to the Korsmeyer-Peppas release kinetics and showed anomalous transport since the constant n was 0.45 > n > 0.89 [21].When anomalous transport and Higuchi kinetics were compared, Higuchi kinetics displayed a closer drug release profile to zero-order kinetics. Based on the obtained results, ER-1 formulation was selected as the candidate to estimate drug release over an entire day (Figure 6).

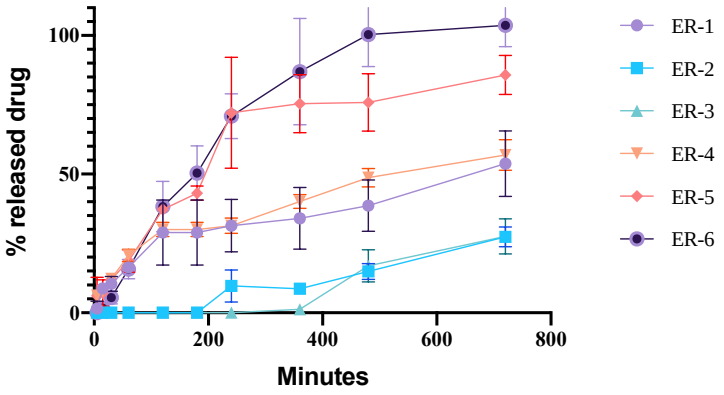


Figure 5. Comparison of the dissolution profiles of ER-1, 2, 4, 5, 6 tablet formulations containing AML.

2.3. Evaluation of kinetics of ER tablets

Six extended-release formulations were studied (Table 4). The dissolution data of ER tablets were used to evaluate the drug release kinetics of the tablets. For a practical solution, the DDSolver programme was used to calculate the drug release kinetics of the tablets [17].

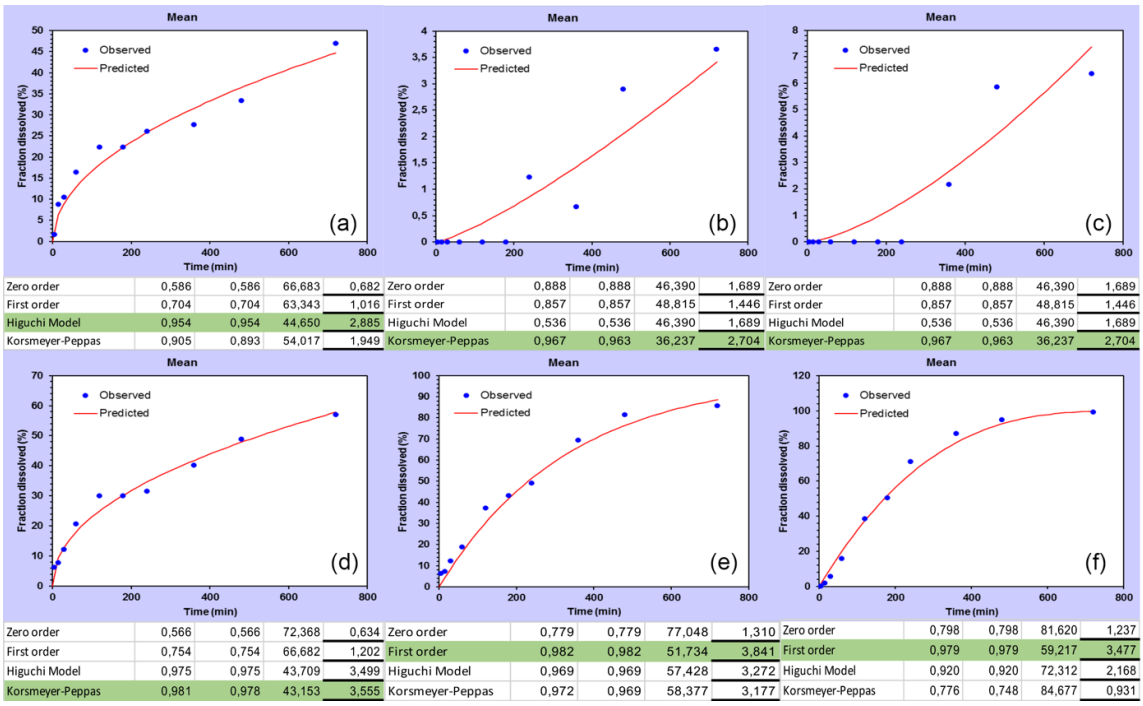
Many different types of HPC with different properties are available on the market. These include HPC-M, HPC-L, and HPC-SL. HPC is used as a binder in the wet granulation process of tablets. However, the long-chain structure enables HPCs to affect tablet drug release kinetics [22]. In our study, the drug release kinetics of six ER tablets are shown in Figure 6.

In this study, the aim was to design a formulation to release 50% of its drug from extended-release tablets within 12 hours. HPC-SL and HPC-M were used in increasing amounts in tablets to achieve these purposes. Our aim was to develop zero-order kinetics formulations; however, unfortunately, we achieved

extended-release tablets instead of tablets with zero-order release kinetics. R-square results are given in Figure 6.

When we look at the drug release kinetics of ER tablets (Figure 6), the drug release kinetics in the ER-1 formulation, in which 30 mg HPC-M was used, fit the Higuchi Model. The Higuchi Model represents the drug release of matrix systems. In ER-2 and ER-3 formulations, where 45 and 60 mg HPC-M was used respectively, drug release took place with Super Case II transport in the Korsmeyer-Peppas model [25]. In this case, the slowly swelling HPC-M in tablets created a barrier around the drug molecules and slowed the release of drug content [23].

HPC-SL was used in formulations ER-4, 5, and 6. HPC-SL had lower viscosity than HPC-M. Therefore, HPC-SL increased the dissolution rate instead of HPC-M. The drug molecules such as HPC-SL and HPC-M could not reduce the dissolution rate by surrounding them.



Zero order	0,586	0,586	66,683	0,682	Zero order	0,888	0,888	46,390	1,689	Zero order	0,888	0,888	46,390	1,689
First order	0,704	0,704	63,343	1,016	First order	0,857	0,857	48,815	1,446	First order	0,857	0,857	48,815	1,446
Higuchi Model	0,954	0,954	44,650	2,885	Higuchi Model	0,536	0,536	46,390	1,689	Higuchi Model	0,536	0,536	46,390	1,689
Korsmeyer-Peppas	0,905	0,893	54,017	1,949	Korsmeyer-Peppas	0,967	0,963	36,237	2,704	Korsmeyer-Peppas	0,967	0,963	36,237	2,704
Zero order	0,566	0,566	72,368	0,634	Zero order	0,779	0,779	77,048	1,310	Zero order	0,798	0,798	81,620	1,237
First order	0,754	0,754	66,682	1,202	First order	0,982	0,982	51,734	3,841	First order	0,979	0,979	59,217	3,477
Higuchi Model	0,975	0,975	43,709	3,499	Higuchi Model	0,969	0,969	57,428	3,272	Higuchi Model	0,920	0,920	72,312	2,168
Korsmeyer-Peppas	0,981	0,978	43,153	3,555	Korsmeyer-Peppas	0,972	0,969	58,377	3,177	Korsmeyer-Peppas	0,776	0,748	84,677	0,931

Figure 6. Comparison of the drug release profile of ER tablets: ER-1(a), ER-2(b), ER-3(c), ER-4(d), ER-5(e), ER-6(f).

2.4. Dissolution studies of chosen ER and IR tablets

ER-1 and IR-5 tablets were studied by placing them in the same dissolution medium (Figure 7). The aim of this study was to achieve a 24-hour drug release of AML and to overcome the fluctuation of AML plasma drug concentrations between dosing intervals. When ER and IR tablets were used together in an *in vitro* study, 75% of the drug was required to be released after 12 hours. The dissolution study results of the selected ER and IR formulations in the same vessel are shown in Figure 7. According to the results of the study, a drug release of 79% occurred at 12 hours.

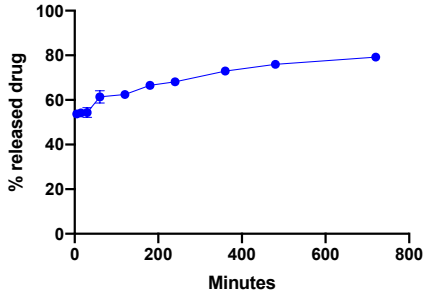


Figure 7. Dissolution profile of IR-5 and ER-1 formulations in the same vessels.

3. CONCLUSION

The aim of this study was to develop an immediate-release tablet and an extended-release tablet containing AML to overcome the fluctuation in plasma drug concentrations between dosing intervals using two different tablet formulations in a single administration for increased patient compliance.

In order to achieve this goal, it was aimed to develop extended-release tablets to release 50% drug at the end of 12 hours. The drug release kinetics of the extended-release tablets were examined with the DDSolver programme. ER-1 formulation was identified as the formulation suitable for the purpose. The dissolution data at 5 minutes was statistically compared to determine the tablet providing the fastest release. Thus, the dissolution data at 5 minutes, which was found to be statistically significant ($p<0.05$), was used to determine the IR tablet that had the highest dissolution rate (IR-5).

Finally, the two selected tablet formulations were studied to reach the targeted drug release (75% drug release at the end of 12 hours) with a dissolution study in the same vessel and 79% drug release was achieved by 12 hours.

In conclusion, multiple-unit systems can be used to develop the release kinetics of conventional tablets. Thus, the fluctuation of plasma drug concentrations can be overcome.

4. MATERIALS AND METHODS

4.1. Materials

Amlodipine besylate, sodium starch glycolate, magnesium stearate, Red iron (gift from Deva İlaç A.Ş.), mannitol (gift from Bilim İlaç A.Ş.), Avicel PH102 (purchased from FMC group), Kollidon CL (purchased from BASF), HPC-M, HPC-SL (purchased from NIPPON soda Co. LTD).

4.2. Methods

4.2.1. Manufacturing process of the tablets

Nine formulations of immediate-release tablets and six formulations of extended-release tablets were produced with the direct compression technique. AML and excipients of each formulation were weighed (Shimadzu ATX220). Then, the bulk was mixed, both before and after the addition of lubricant, for five minutes using a V type laboratory scale mixer.

After mixing the formulations, all tablets were weighed individually. Then, the tablets were pressed into a 6-mm flat-faced punch in a Kaan Kalıp eccentric tablet press.

Compression pressures were adjusted by measuring the hardness of tablets that were pressed at that moment. All formulation batches were inspected with a Holland tablet hardness tester C50 and all batches of formulations were pressed individually with calibrated pressure. The calibration of tablet hardness was adjusted to 6 – 9 kg. However, some formulations did not meet these hardness values because of the compressibility limits of some excipients in the formulation.

Each formulation contained 6,944 mg Amlodipine besylate equivalent to 5 mg of Amlodipine.

4.2.2. Characterization of the tablets

Dissolution tests

Immediate-release (IR) tablets

0.01 N HCl (or pH 2) was selected as the dissolution medium, a recommended dissolution medium in FDA documentation for tablets including amlodipine besylate [24]. A paddle apparatus at 50 rpm and Sotax dissolution device were used in the dissolution test. The dissolution study was conducted at 37 ± 2°C in a 900-mL dissolution medium. Samples were taken at 5, 15, 30, and 60 minutes [25]. The ingredients of immediate-release tablets are shown in Table 3.

Extended-release (ER) tablets

0.01 N HCl (pH 2), 900 mL for the first two hours and pH 6.8 phosphate buffer, 900 mL between 2 – 12 hours was selected as the dissolution medium. Samples were taken at 5, 15, 30 and 60 minutes and 2, 3, 4, 6, 8 and 12 hours. The change in pH after 2 hours was made by pouring the pH 2 dissolution medium carefully and then adding a 900-mL pH 6.8 dissolution medium into the same vessel. Caution was exercised to not drop any ER tablets while pouring the dissolution medium. The same conditions (paddle speed, paddle number

that was used and temperature of the dissolution medium) were applied to both ER tablets and IR tablets [16]. The ingredients of extended-release tablets are shown in Table 4.

Table 3. Formulation of immediate-release tablets (mg).

Ingredients of IR tablets	IR-1	IR-2	IR-3	IR-4	IR-5	IR-6	IR-7	IR-8	IR-9
AML	6.994	6.994	6.994	6.994	6.994	6.994	6.994	6.994	6.994
Primojel	10	10	10	20	30	30	-	30	30
Kollidon CL	10	20	30	10	10	-	30	10	10
Mannitol	20	20	20	20	20	20	20	-	53.06
Avicel PH102	53.056	43.056	33.056	43.056	33.056	43.056	43.056	53.056	-
Red Iron	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Total	101.5	101.5	101.5	101.5	101.5	101.5	101.5	101.5	101.5

Table 4. Formulation of extended-release tablets (mg).

Ingredients of ER tablets	ER-1	ER-2	ER-3	ER-4	ER-5	ER-6
AML	6.994	6.994	6.994	6.994	6.994	6.994
HPC-M	30	45	60	-	-	-
HPC-SL	-	-	-	30	45	60
Avicel PH102	62.056	47.056	32.056	62.056	47.056	32.056
Magnesium Stearate	1	1	1	1	1	1
Total	100	100	100	100	100	100

IR and ER tablets together in the same vessel

All conditions were the same as in the dissolution test with ER tablets.

Analytical methods and validation

AML was scanned in the range of 200-700 nm to detect the wavelength of maximum absorption in pH 2 and pH 6.8 media. The maximum absorption of AML was recorded at 201, 238 and 366 nm. Dissolution samples were read at 238 nm in a UV-VIS spectrophotometer (Mettler Toledo UV5) and the amount of AML was calculated using the absorbance/concentration equation that was already found for AML at pH 2 and pH 6.8.

After sampling 5 mL of dissolution medium, an equal volume of fresh dissolution medium was added to maintain sink conditions. Samples were filtered through a 0.45-µm Millipore filter. The methods were validated according to ICH guidelines for linearity, precision, accuracy, limit of detection and limit of quantification.

Tablet hardness

After compression of IR and ER tablets, 10 tablets of each formulation were crushed in a Holland C50 tablet hardness tester and recorded. The measuring unit of crushing strength was kg/cm^2.

The mean values and standard deviations of crushing strength of the tablet formulations were calculated.

Disintegration study

IR formulations were tested with a Pharma Test disintegration tester in a 900-mL 0.01 N HCl medium. Six tablets were disintegrated for each formulation and the disintegration time was recorded based on European Pharmacopoeia 7.0 (EP) regulations.

Tablet size

The diameter and thickness values of tablets were measured with a digital caliper. Ten tablets were measured and recorded. Mean and standard deviation values of tablet sizes were calculated.

Weight variation test of tablets

Twenty tablets were weighed. According to EP, the mass of no more than 2 tablets can deviate from the average mass by more than 7.5 percent.

4.2.3. Statistical comparison

The dissolution results of F1-9 formulations were compared using SPSS (Version 23) ANOVA and Tukey's test was used as the post-hoc test.

4.2.4. Drug release kinetics of extended-release tablets

The drug release kinetics of ER formulations were calculated using the DDSolver software programme [26].

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Conflict of interest statement: The authors declared no conflict of interest.

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