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COMPARISON OF SINGLE- AND MULTI-STAGE EXTRUSION VERSUS PRESS-COATING TECHNIQUE IN FORMULATION OF MODIFIED-RELEASE TABLETS WITH THEOPHYLLINE

Popova T., Petkova V*. and Dimitrov M.

Faculty of Pharmacy, Medical University of Sofia, Bulgaria.

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***Corresponding Author**
Petkova V.
Faculty of Pharmacy,
Medical University of Sofia,
Bulgaria.

ABSTRACT

Theophylline has been used in the treatment of respiratory diseases such as asthma and COPD for more than 80 years. It is still a common reported drug, especially for patients with a pronounced clinical picture due to its easy application and low price. The bronchodilating action of theophylline makes the drug useful in the chronic treatment of bronchial asthma, but its narrow therapeutic concentration range and variable pharmacokinetics make dosing management of the drug difficult, which requires utilization of modified release drug dosage forms. One approach to increase the effectiveness of pharmacotherapy is to administer medications while they are most effective and/or tolerable. The principles of chronotherapy can be applied by designing and characterizing drug delivery systems that synchronize drug release with the rhythm of disease activity. Time-controlled release rate can be achieved in many ways, but press-coating technology and multiple-unit pellet systems (MUPS) are one of the most promising techniques. For the purpose of the present study – development of chronopharmaceutical system for treatment of nocturnal asthma, nine formulations tablets prepared from pellets via single- (E1-1-E3-1), two- (E1-2-E3-2) and three-stage (E1-3-E3-3) extrusion and nine formulations single- (T1-1-T3-1), two- (T1-2-T3-2) and three-layered (T1-3-T3-3) press-coated tablets using different polymer blends were prepared, characterized and compared. Formulations with HPMC release slower than formulations with CMC Na and increasing viscosity grade of HPMC, leads to decreasing in release rate. Moreover, fastest is the release rate from single-extruded pellets and slowest – from three-stage extruded pellets. Comparing method of preparation – press-coating technique gives faster release of API than multi-stage extrusion. Among all

formulations, formulations E1-3, E2-3, E3-3 and T2-3 exhibit the desired chronotherapeutical release profile – taken before bedtime they deliver API between midnight and early morning hours when asthma incidents are with higher frequency.

1. INTRODUCTION

Over the last few decades, conventional formulations have been widely used to treat various conditions. These formulations typically provide an immediate or rapid release of the drug without the ability to control the process.[1,2]

In the early 1990s, second generation modified-release formulations have been developed in which sustained or delayed drug release aimed to reduce concentration fluctuations in order to increase the efficacy of the drug and minimize the side effects. Modified-release drug systems are expected to provide a reduced dosing frequency and improved compliance of the patient compared to the conventional tablets.[3, 4, 5]

Study of influence of biological rhythm on the effects of medication is known as chronopharmacology while the science of study of biological rhythms is known as chronobiology.

Bronchial asthma (BA) is a common respiratory disease among both adults and children that affects more than 300 million people worldwide and causes substantial morbidity.[6,7] Symptoms of asthma consist of recurrent episodes of acute bronchoconstriction causing dyspnea, difficult breath, cough, chest tightness, wheeze and rapid respiration combine with airway inflammation.[8]

Theophylline is a bronchodilator and it has also been reported to suppress airway inflammation.[9, 10] However, its narrow therapeutic concentration range (10–20 μg/ml) and variable pharmacokinetics make dosing management of the drug difficult and this requires utilization of modified release drug dosage forms, which give stable serum theophylline concentration.[11]

For patients with chronic asthma, including patients with marked asthma requiring inhaled corticosteroids, many studies have confirmed that theophylline reduces the incidence and severity of symptoms, including nocturnal exacerbations, and reduces the need for inhaled beta-2-agonists. Theophylline is also shown to reduce the need for oral prednisolone to relieve exacerbations that are not only controlled by bronchodilators in asthmatics.[12-16]

One approach to increase the effectiveness of pharmacotherapy is to administer drugs while they are most effective and/or best tolerated. The principles of chronotherapy can be realized by choosing the right time for conventional tablets and capsules, or designing and characterizing drug delivery systems to synchronize drug release to the rate of disease activity.[17] Asthmatic chronotherapy requires targeted delivery of theophylline in unequal amounts over 24 hours to achieve an increased concentration during the night-time (midnight – early morning hours) when the risk of bronchial asthma is greatest and a decreased concentration during the day when the risk of a bronchial asthma attack is lower.[18]

Chronopharmaceutical conditions require the design of a system from which the drug is not released rapidly, immediately release, but as a "pulse" after a certain time.[19] Such systems are known as pulsatile drug delivery systems (PDDS). PDDS have been developed in close connection with the newly-established principles of chrono pharmacotherapy. This delivery of drugs is of great interest, because it is possible to ensure the supply of an exact amount drug at a specific time and at a specific site. The newest developed drug delivery systems are consistent with biological rhythms and medication delivery is tailored to the peak in the manifestation of the symptoms of the disease.[20, 21]

Contin® chronopharmaceutical technology is used in the preparation of matrix sustained-release Uniphyl®/Uniphyllin® tablets with theophylline.[22] This technology is based on the molecular coordination complexes formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group.[19, 23] Unfortunately, our research discovered that the release rate of theophylline from Uniphyllin® tablets is too slow and they may be do not provide satisfactory lag time.

There are a lot of promising technologies that can provide pulsatile release – layered systems, time-controlled explosion systems, sigmoidal release systems, press-coated systems, miscellaneous systems, core-cup-tablets, multiparticulate systems, pulnicap systems, infusion pumps, etc.[24-26]

Extrusion is a multistage process that is used to produce cylindrical particles of approximately the same size. The method is mainly used to produce the so-called multiple unit dosage systems intended for modified release. The greatest advantage of extrusion over other methods of making drug-loaded pellets is the possibility of including a large amount of drug substance without getting too large pellets (i.e., need of minimal amounts of excipients).

With pellets, it is very easy to achieve a modified release by simply preparing and then combining in capsules or tablets several different pellet fractions with different release profile to give immediate, intermediate or delayed release. Furthermore, these compact multiparticulate systems (pellets) are much less dependent on stomach emptying and intestinal transit than individual units such as coated tablets.

Press-coating technique is the most usable techniques for preparation of time-controlled release systems, because of its indisputable advantages.[27, 28]: no need of solvents, protection of hygroscopic, light sensitive, oxygen and acid labile drugs, isolation of incompatible drugs from each other, fast and simple manufacturing.[29, 30] Usually press-coated tablets comprise inner core surrounded by one or more outer layers that dissolve or disintegrate slowly to produce lag-time. Depending on the polymers used in this system, location of inner core, inner core – outer shell ratio, compression pressure and other formulation variables, they can deliver the drug after swelling and/or eroding of coating shell, obtaining time-controlled release.[31, 32]

Utilization of multiple-unit pellet systems (MUPS) are gaining much more importance over single-unit dosage forms due to their potential advantages: increased bioavailability; predictable, reproducible with short gastric residence time; no risk of dose dumping; reduced risk of local irritation.[33, 34] Their main advantage is the flexibility to blend pellets with different compositions or release patterns in order to achieve desired release rate.[35] Among all of the methods for preparation of pellets, extrusion/spheronization technique enables high drug loading.[36, 37] Multi-stage extrusion technology is kind of extrusion that gives the opportunity to achieve pulsatile release profile with simply re-extruded the already prepared pellets with utilization of different polymers without using additional equipment.

2. MATERIALS AND METHODS

2.1 Materials

Theophylline monohydrate, carbohymethylcellulose (50-200 cP) and hydrohypropylmethylcellulose with different viscosity grade (4000 cP and 80-120 cP) were obtained from Sigma Aldrich, Germany.

2.2 Methods

2.2.1 Preparation of tablets from pellets via single-, two- and three-stage extrusion

The technological scheme for preparation of pellets via single-stage extrusion includes weighting (electronic balance), sieving (0,5 mm mesh size sieve) and mixing (homogenizer - 10 min, 6 rpm) of API (theophylline) and polymer (HMPC 4000 cP, HPMC 80-120 cP or CMC Na 50-200 cP). The mixture was then wetted with the needed amount of 95% ethanol and extruded through radial screw-feed extruder (4M8Trix, Procept, Belgium) with die diameter 0,8 mm and 35 rpm feed rate of wet mass (fig. 1 and 2).

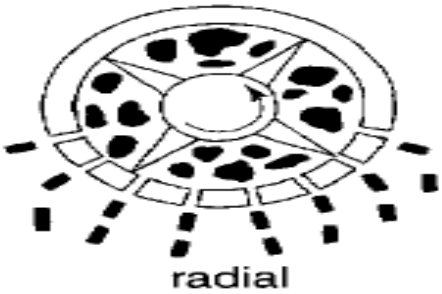

Fig. 1: Radial die of screw-feed extruder.

Fig 2: Radial screw-feed extruder (4M8Trix, Procept, Belgium)

The obtained wet extrudate was dried in tray drier till achieving loss on drying 2% and then half of pellets were compressed on Erweka AR401 single stroke tablets press with compression tooling for flat round tablets with diameter of 5 mm and average mass of one tablet – 80 mg ±7.5% (formulations E1-1-E3-1).

The other half of the prepared pellets via single-stage extrusion (E1-1-E3-1) was then used for preparation of two-stage extruded pellets. The mixture of single-stage extruded pellets with additional adding of polymer (HMPC 4000 cP, HPMC 80-120 cP or CMC Na 50-200 cP) was wetted with 95% ethanol and extruded again through the same extruder but with bigger die diameter - 1,0 mm. The obtained extrudate in tray drier till achieving loss on drying 2% and then half of the pellets were compressed - diameter of 10 mm and average mass of one tablet – 300 mg ±5% (formulations E1-2-E3-2).

Three-stage extruded pellets were prepared from two-stage extruded with additional adding of polymer by the same methodology, but with the biggest extruder die diameter – 1,2 mm. Tablets prepared from them were with diameter 13 mm and average tablet mass – 600 mg ±5% (formulations E1-3-E3-3) (fig.3).

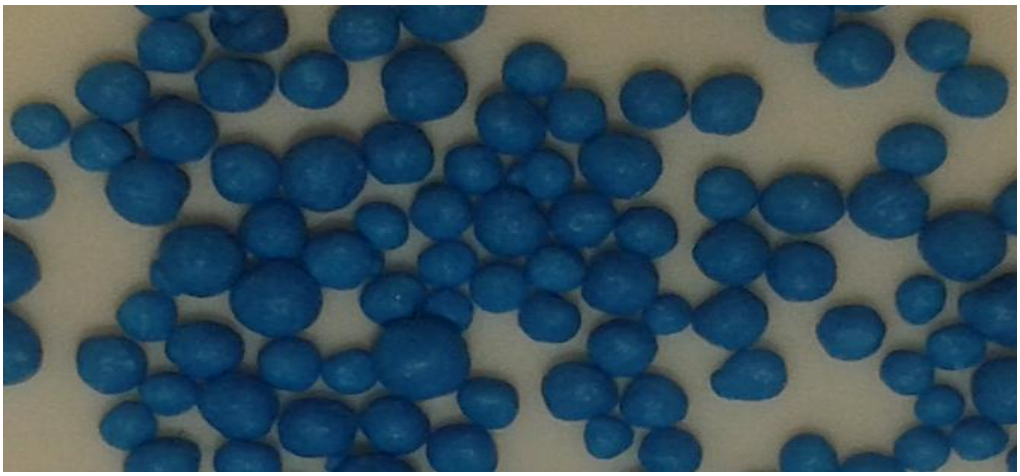

Fig 3: Pellets prepared via single-, two- and three-stage extrusion.

All of the obtained tablets comply with the criteria for uniformity of mass (%RSD≤5), uniformity of content, resistance to crushing and friability (≤1%). Their composition is given in table 1.

Table 1.

Composition of tablets prepared from pellets via single-stage extrusion		
E1-1	**E2-1**	**E3-1**
Theophylline	Theophylline	Theophylline
HPMC 4000 cP	HPMC 80-120 cP	CMC Na 50-200 cP
Composition of tablets prepared from pellets via two-stage extrusion		
E1-2	**E2-2**	**E3-2**
+ HPMC 80-120 cP	+ CMC Na 50-200 cP	+ HPMC 4000 cP
Composition of tablets prepared from pellets via three-stage extrusion		

E1-3	E2-3	E3-3
+ CMC Na 50-200 cP	+ HPMC 4000 cP	+ HPMC 80-120 cP

2.2.2 Preparation of single-, two- and three-layered tablets via press-coating technology

Three-layered press-coated tablets consist of a core and two outer layers (fig. 4). Their composition is given in table 2.

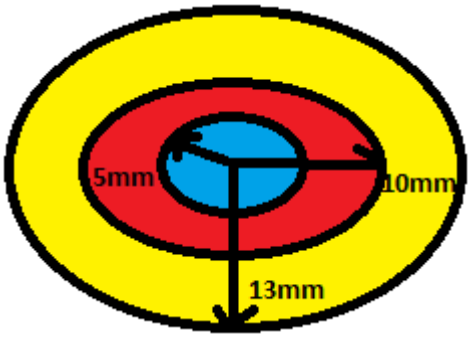

Fig. 4 Graphic view of multi layered press-coated tablet.

Table 2.

Composition of single-layered tablets		
T1-1	**T2-1**	**T3-1**
Theophylline	Theophylline	Theophylline
HPMC 4000 cP	HPMC 80-120 cP	CMC Na 50-200 cP
Composition of two-layered press-coated tablets		
T1-2	**T2-2**	**T3-2**
+ Theophylline	+ Theophylline	+ Theophylline
+ HPMC 80-120 cP	+ CMC Na 50-200 cP	+ HPMC 4000 cP
Composition of three-layered press-coated tablets		
T1-3	**T2-3**	**T3-3**
+ Theophylline	+ Theophylline	+ Theophylline
+ CMC Na 50-200 cP	+ HPMC 4000 cP	+ HPMC 80-120 cP

The technological scheme for preparation of single-layered tablets, or so called core tablets, includes weighting (electronic balance), sieving (0,5 mm mesh size sieve) and mixing (homogenizer - 10 min, 6 rpm) of API (theophylline) and polymer (HMPC 4000 cP, HPMC 80-120 cP or CMC Na 50-200 cP). The obtained mixture was then compressed on Erweka AR401 single stroke tablets press with compression tooling for flat round tablets with diameter of 5 mm and average mass of one tablet – 80 mg ±7.5% (formulations T1-1-T3-1).

One-half of the prepared cores (T1-1-T3-1) were then used for preparation of two-layered press-coated tablets (1-st outer layer). Powder mixture for preparation of 1-st outer layer (theophylline plus polymer - HMPC 4000 cP, HPMC 80-120 cP or CMC Na 50-200 cP) was

compressed with the core tablet (T1-1-T3-1) in its center using 10 mm punch to an average tablet mass – 300 mg ±5% (formulations T1-2-T3-2).

The three-layered press-coated tablets (2-nd outer layer) were prepared the same as 1-st outer layer: powder mixture, containing theophylline and polymer was compressed with the two-layered tablet (T1-2-T3-2) in its center using punch diameter – 13 mm with average tablet mass - 600 mg ±5% (formulations T1-3-T3-3). The technology of press-coating is shown in fug. 5.

As it can be seen from table 1. and 2. the code of adding polymers in each layer of multi-layered press-coated tablets is the same as in each stage of extrusion in tablets prepared from pellet via multi-stage extrusion.

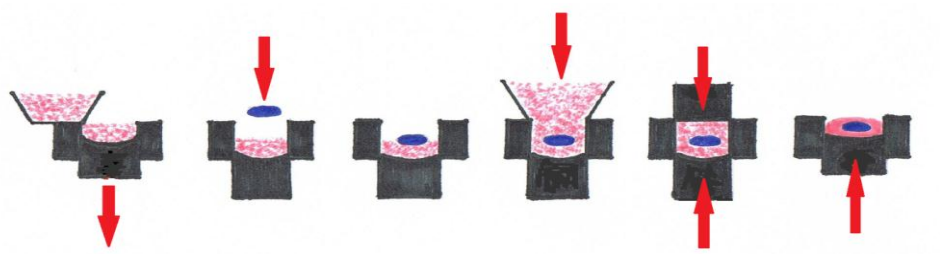

Fig. 5.

2.2.3 In-vitro dissolution study of obtained formulations

In order to investigate the influence of type and viscosity grade of polymers and method of preparation (extrusion or press-coating) on drug release from prepared formulations, in-vitro dissolution studies were conducted using Dissolution tester RC-8D, PRC - Apparatus 2 – Paddle Apparatus (Ph.Eur.,2.9.3.), according to modified test from USP 37 for "Capsules with sustained/prolonged release – Test 9". The tests were carried out in two medium - 900 ml of 0,1 N hydrochloric acid without enzymes (pH-1,2) for one hour and phosphate buffer (pH-6,8) for the rest 9 hours, at (37 ± 0,5)^{o}C and agitated at 50±2 rpm with six tablets per study. Samples of 5 ml were withdrawn with media replacement at regular intervals (30 min, 1h, 2,3,4,5,6,7, 8, 9 and 10h), filtrated through 1-2 µm filters, diluted when needed (1,0 ml from the sample till 10,0 ml for the samples till 3-rd hour and 1,0 ml till 25,0 for the rest samples with appropriate media) and assay spectrophotometrically at λ_{max} 273 nm. The amount of API (theophylline) dissolved (Q%), has been measured via standard curve method, according to the following equation.

Q%=(A*V*C*100)/(b*X), where

A – absorption, nm

V – medium volume, ml

C - dilution

b – the slope of the standard curve

X – the amount of theophylline in each tablet, mg

3. RESULTS AND DISCUSSION

3.1 Evaluation of the influence of type and viscosity grade of polymer on drug release from obtained formulations

The average values (from 6 tablets) of amount of theophylline released (Q%) during specified time intervals from dissolution study of the three formulations tablets prepared from pellets via single-stage extrusion (E1-1-E3-1) and three formulation single-layered tablets (T1-1-T3-1 are shown in fig. 6 and 7. ; X-axis contains time in hours and Y-axis - % of API released. Statistical processing of results from the tests established RSD<20% in the first time interval and RSD<10% for the following time intervals for all formulations.

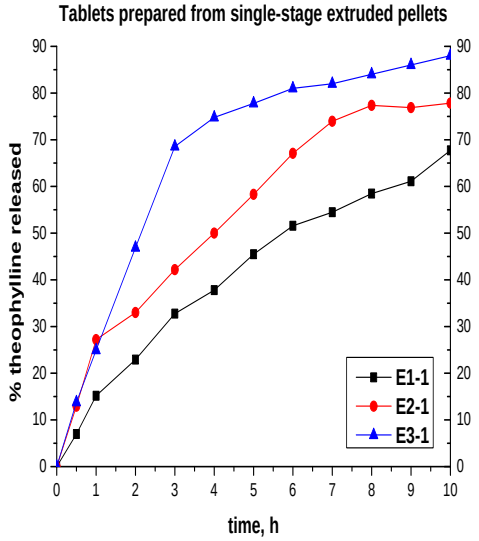

Fig. 6.

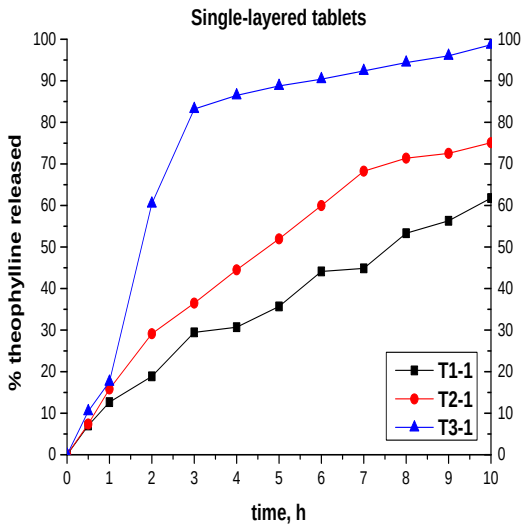

Fig. 7.

Results from dissolution studies point out the significant influence of type and viscosity grade of polymers on drug release. As it can be seen from fig. 5 and 6, increasing viscosity grade of HPMC (from HPMC with 80-120 cP to HPMC with 4000 cP) in tablets, prepared via both technology, leads to increasing in swelling and decreasing in release rate of active pharmaceutical ingredient (API) – theophylline. That is why the release rate of E2-1 and T2-1

(HPMC 80-120 cP) is faster than respectively E1-1 and T1-1 (HPMC 4000 cP). Between two polymers - HPMC and CMC Na, the last one swells less and exhibits faster release rate (formulations E3-1 and T3-1 release fastest). Moreover, with increasing of viscosity grade of HPMC the linearity of the curve increases, which is an indication that it is more likely to obtain zero-order kinetics release rate from tablets with HPMC with higher viscosity grade.

3.2 Evaluation of the influence of the stage of extrusion on drug release from obtained tablets prepared from pellets via multi-stage extrusion

The influence of the stage of extrusion (single-, two- and three-stage extrusion) on drug release is presented in fig. 8.

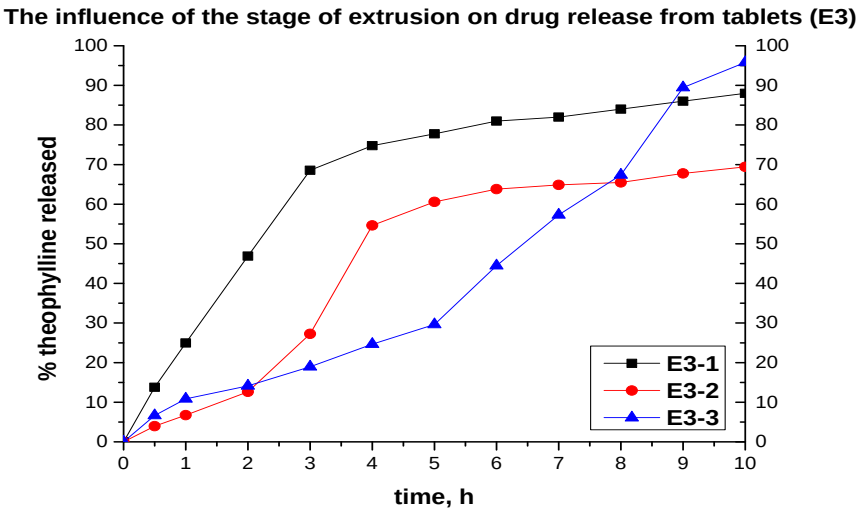

Fig. 8.

As it can be seen from the drug release profiles (fig. 8) the stage of extrusion plays significant role in drug release. In the order single-stage, two-stage and three-stage extrusion, the release of theophylline decrease. The slowest is the release rate from tablets prepared from pellets via three-stage extrusion (E1-3-E3-3) and the fastest is the release rate from tablets prepared from pellets via single-stage extrusion (E1-1-E3-1). This can be explained with the fact that during two- and three-stage extrusion only polymers were added, without theophylline (theophylline is presented only in single-stage extruded pellets). In that way API is protected from the entry of water by the presence of swelling polymers added at two- and three-stage extrusion, which leads to decreasing initial release (lag-time) and slowing of the release rate. In that case, three-stage extruded pellets act like three-layered coated pellets (fig. 9).

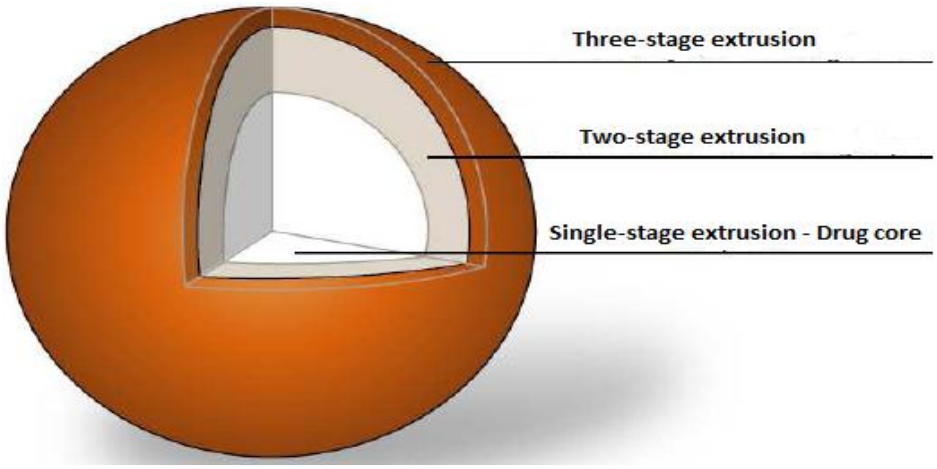

Fig. 9. The schematic view of multi-stage extruded pellet

3.3 Evaluation of the influence of the number of layers on drug release from obtained press-coated tablets

The influence of the number of layers on drug release from press-coated tablets is not as simple and linear as in stage of extrusion in tablets prepared from pellets. This is because in each layer of press-coated tablets, not only polymer but also theophylline was added. The influence of the type and viscosity grade of polymers on drug release keeps the same trend.

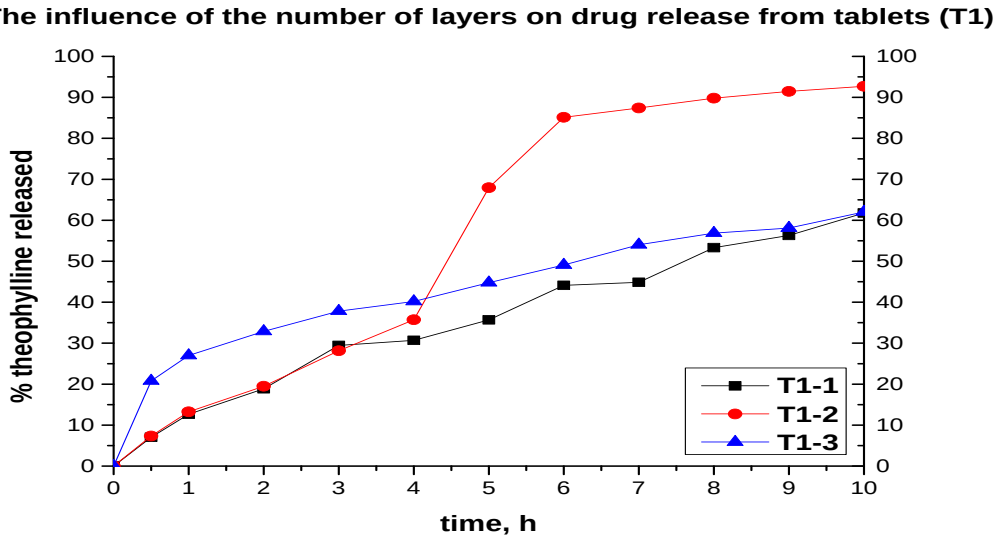

Fig. 10.

The slowest release of formulation T1-1 (single-layered tablet), compared to T1-2 (two-layered press-coated tablet) and T1-3 (three-layered press-coated tablet) is due to the presence of only of HPMC 4000 cP in its composition (fig. 10). On the other hand, the fast initial release from formulation T1-3 (three-layered press-coated tablet) is because of CMC Na 50-200 cP in its 2-nd outer layer.

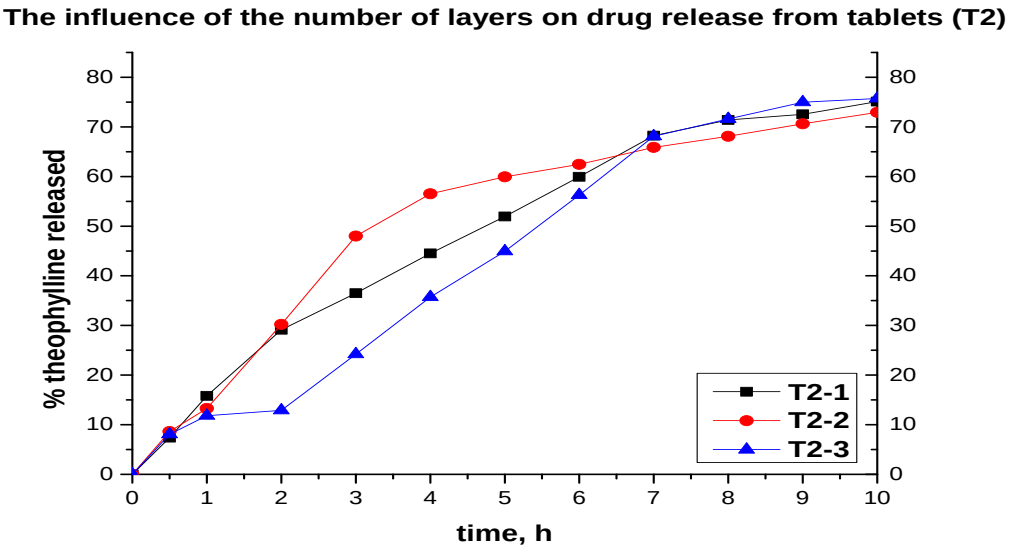

Fig. 11.

Comparing formulations T2-1-T2-3, it can be conclude that fast initial release from T2-2 (two-layered press-coated tablet) is again due to the CMC Na 50-200 cP in its 2-nd outer layer, whereas the slow release from formulation T2-3 - because of the presence of HPMC 4000 cP (fig. 11).

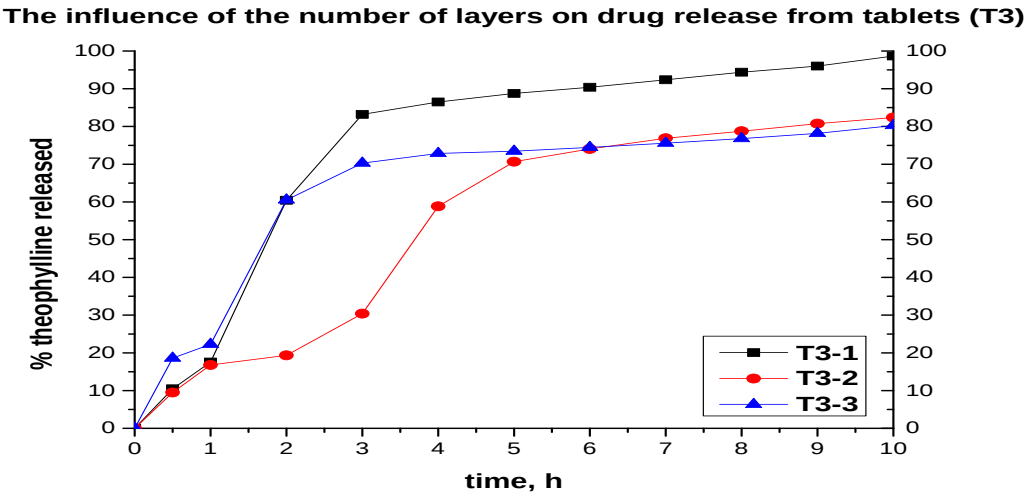

Fig. 12.

The last three group of formulations (T3-1-T3-3) express the same trend: the fast initial release from formulation T3-1 (single-layered tablet) is because of CMC Na and the slow release of T3-2 (two-layered press-coated tablet) – due to the HPMC 4000.

It can be concluded that the release from press-coated tablets is depended mainly on the composition of the last outer layer.

3.4 The influence of the method of preparation of tablets (extrusion versus press-coating) on drug release

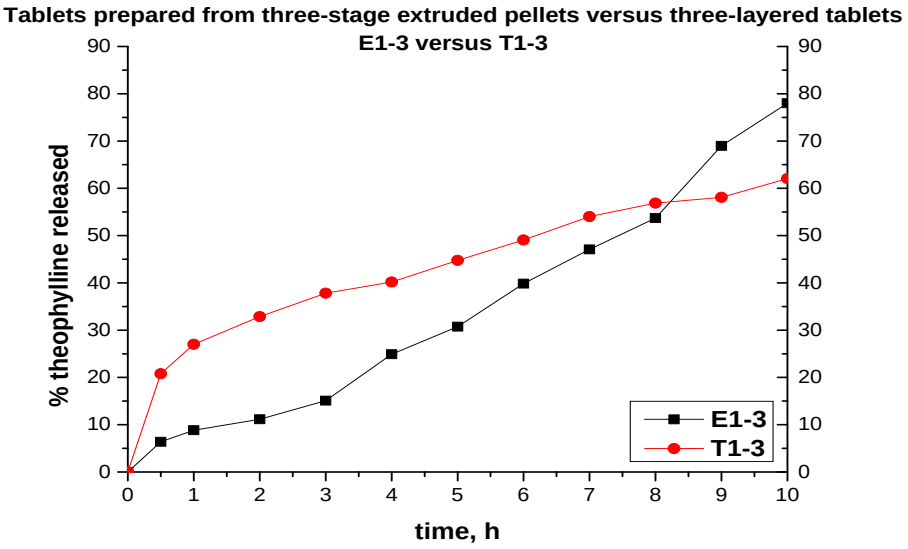

Fig. 13.

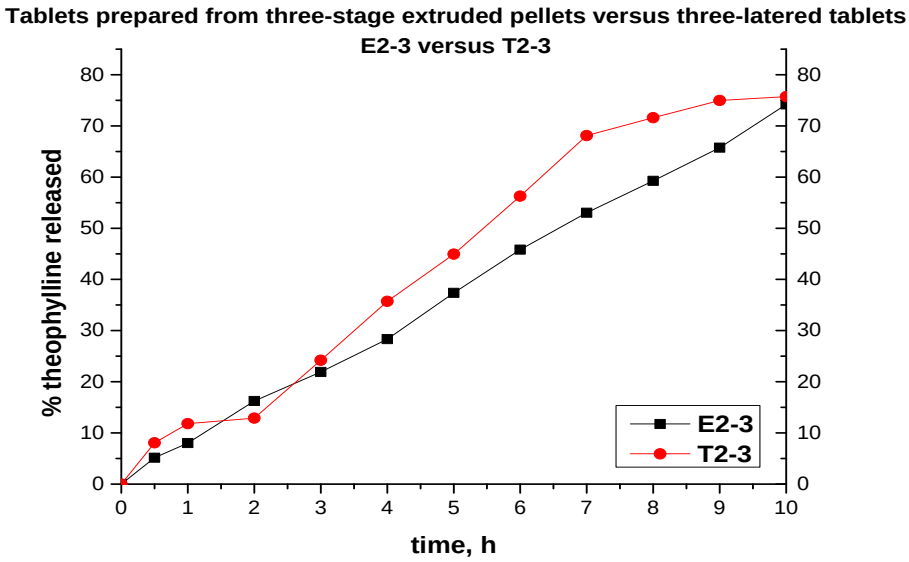

Fig. 14.

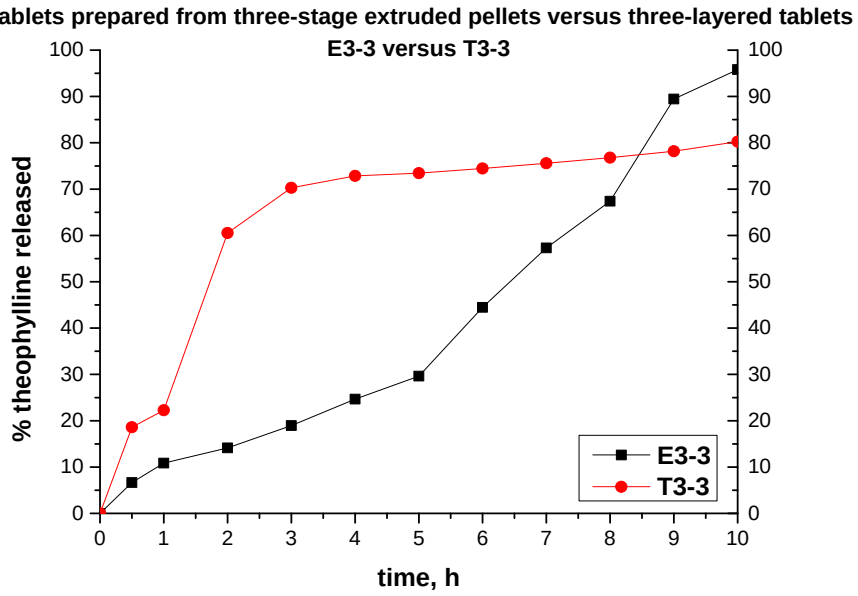

Fig. 15.

As it can be seen from fig. 13-15 the method of preparation is of great importance to drug release. Comparing tablets prepared from three-stage extruded pellets to three-layered press-coated tablets, it can be conclude that release rate of theophylline from last one is faster. This can be explained with the fact that API in pellets was placed only in single-stage extruded pellets and during next stage of extrusion, only polymers were added which leads to slowing the release rate and reducing initial release. On the other hand, each layer of multi-layered press-coated tablets contains not only polymer but also theophylline, which is the reason of burst effect from these formulations.

All of the formulations, prepared via three-stage extrusion and three-layered press-coating techniques (except from formulations T1-3 – Q+5%<70% and T3-3 – too fast initial release) are promising as chronopharmaceutical system. They have slow initial release - below 15% for the first two hour (sufficient lag-time) and then release satisfactory ((Q+5%≥70%) for the rest 8 hours. These systems, taken before bedtime, will deliver the API (theophylline) between midnight and the early morning hour when the asthma incidents are more probable to happen.

4. CONCLUSION

Data, obtain from the in-vitro dissolution study of nine formulations tablets prepared from pellets via single- and multi-stage extrusion and nine formulations single-, two- and three-

layered press-coated tablets confirm the expectations about the influence of type and viscosity grade of polymers on API's release behavior - formulations with HPMC release slower that formulations with CMC Na and increasing viscosity grade of HPMC – from HPMC 80-120 cP to HPMC 4000 cP, leads to decreasing in release rate. Comparing tablets prepared from pellets via single-, two- and three-stage extrusion, it can be conclude that the fastest is the release rate from single-extruded pellets and slowest – from three-stage extruded pellets. Moreover, method of preparation plays a significant role in drug release. Tablets prepared from three-stage extruded pellets exhibit slower release rate of theophylline than three-layered press-coated tablets, which is due to the presence of API only at single-stage extrusion, also leading to reducing the initial release (lag-time). Among the all formulations, formulations E1-3, E2-3, E3-3 and T2-3 satisfy the requirements of chronotherapy. These systems are design, by taken before bedtime, to have sufficient lag-time, delivering theophylline between midnight and early morning hours when asthma attacks are most probable to happen. This complies with the main principle of chronotherapy – synchronization of drug concentration to rhythms in disease activity.

ACKNOWLEDGMENT

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