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EXTRUSION - A POTENTIAL KEYSTONE SOLUTION FOR PREPARATION OF CHRONOPHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Bronchial asthma displays significant circadian variation at onset or exacerbation of symptoms (50-100 time more common between midnight and early morning hours with peak of bronchoconstriction at 4.00 am), which requires specific administration timing and creating chronopharmaceutical systems which can release the drug within a short/prolonged period of time, immediately after a predetermined lag-time – pulsatile-release drug delivery systems. 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, like Contin® chronopharmaceutical technology, used in Uniphyl®/Uniphyllin® tablets. Unexpected, our recent in vitro study revealed that the release rate of theophylline from Uniphyllin® tablets is too slow and there is potential possibility that they could not provide satisfactory lag time. Utilization of multiple-unit pellet systems (MUPS) are one of ways that pulsatile-release or so called "time clock systems" can be achieved. Multi-stage extrusion (two or three stages) approach technology gives the opportunity to achieve pulsatile release profile with simple re-extrusion of the conventional or modified release pellets prepared by one stage extrusion. The present study compromises preparation and characterization of nine formulations tablets by tabletting of pellets prepared after single- (E1-1-E3-1), two-(E1-2-E3-2), or three-stages (E1-3-E3-3) extrusion with application of different polymer blends. 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. Among all formulations, formulation E3-3 (tablet prepared from pellets via three-stage extrusion) exhibits the desired

chronopharmaceutical release profile. This system is designed, by taken before bedtime, to deliver API between midnight and early morning hours when asthma incidents are with higher frequency, which fully complies with the main principle of chronotherapy – synchronization of drug concentration to rhythms in disease activity.

KEYWORDS: chronotherapy, extrusion, asthma.

1. INTRODUCTION

Despite the indisputable advantages of modified release drug dosage forms versus conventional drug dosage forms, the treatment of many conditions with them is sometimes inappropriate and inapplicable, because of the drug resistance, tolerance and the impossibility to deliver the active pharmaceutical ingredient (API) in accordance with the chronopharmacological requirements of the disease.[1] That is why recently studying of biological circadian rhythms is under serious attention.[2] Chronobiology is the study of biological rhythms and its principle can be implemented into the fields of medicine, pharmacology and drug delivery.[3-4] Chronopharmaceutics is the delivery of medicines in a manner that release the drug according to the biological rhythms and requirements of the disease therapy.[5-6] From the viewpoint of chronotherapy, the application of biological rhythm to pharmacotherapy may be accomplished by two ways. First one is by appropriate timing of conventionally formulated tablets and capsules - drugs taken before bedtime, and the second one - creating innovative drug delivery systems that synchronize drug concentrations to rhythms in disease activity.[7] This kind of systems are relevant in the treatment of diseases in which zero-order released kinetics is not desirable, because of the specific timing of symptoms' peak. By appropriate design chronopharmaceutical systems can release the drug within a short/prolonged period of time, immediately after a predetermined lag-time[8] – pulsatile-release drug delivery systems.[9-10]

Bronchial asthma (BA) is a chronic inflammatory disorder of the airways that affects more than 300 million people worldwide and causes substantial morbidity.[11] Symptoms of asthma include recurrent episodes of acute bronchoconstriction causing difficult breath, cough, chest tightness, wheezing and rapid respiration.[12] BA is lifelong disease and it cannot be cured, but with proper treatment there is a possibility for improvement patients' quality of life. Bronchial asthma displays significant circadian variation at onset or exacerbation of symptoms. The chronobiological features of asthma show that asthma exacerbations are 50-100 time more common between midnight and early morning hours with peak of

bronchoconstriction at 4.00 am.[13- 15] In patients with nocturnal asthma, decrement in lung function during night occurs with increased airway hyper responsiveness and airway inflammation leading to cough and dyspnea, which disrupt sleep.[16] Nocturnal symptoms of asthma are associated with increased morbidity and a lower quality of life. Drugs that were developed on the basis of chronopharmacology requirements are now available for adequate management of the nocturnal exacerbation of asthma. For the purpose of improving the efficacy and reducing adverse effects, the administration time and specific drug delivery system are arranged considering the status and symptoms of the diseases.[17] Most of the drugs currently used for chronotherapy of asthma are administered once at night with the goal of preventing chronic airway inflammation or airways obstruction. A single dose before bedtime contributes to improve patients' compliance and better self-management of asthma. The bronchodilating action of theophylline makes the drug useful in the chronic treatment of bronchial asthma.[18] 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.[19] Contin® chronopharmaceutical technology is basically used in the preparation of sustained-release Uniphyl®/Uniphyllin® tablets with theophylline.[20] In this technology, molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group.[16][21] Unexpected, our recent in vitro study revealed that the release rate of theophylline from Uniphyllin® tablets is too slow and there is potential possibility that they could not provide satisfactory lag time.

Utilization of multiple-unit pellet systems (MUPS) are one of ways that pulsatile-release or so called “time clock systems” can be achieved.[22] MUPS are gaining much favor over single-unit dosage form because of their benefits: increased bioavailability; predictable, reproducible with shorter gastric residence time; reduced or even no risk of dose dumping; reduced risk of local irritation.[23] Their main advantage is the flexibility to blend pellets with different compositions or release patterns in order to achieve desired release rate. Because of their smaller particle size these systems are capable of passing through the GI tract easily, leading to less inter- and intra-subject variability.[24] Several technologies for preparation of MUPS are available (spray-drying, extrusion/spheronization, film-coating technology, etc.), but extrusion/spheronization techniques has the advantages of high drug loading capacity without producing extensively large particles.[25] By additionally coating of prepared spheroids or utilization of multi-stage extrusion it’s possible to be prepared variety of

formulations with different release profile. Multi-stage extrusion technology gives the opportunity to achieve pulsatile release profile with simply re-extruded the already prepared conventional release or modified release pellets twice or triple with utilization of different polymers. In that way multi-layered pellets with pulsatile release can be obtain without the need of using additional equipment. Prepared MUPS then can be compressed into tablets or filled into capsules for better handling.[26]

Among the most used polymers for preparation of pellets intended for modified release via extrusion/spheronization are cellulose derivates – hydoxypropylmethycellulose (HPMC), carboxymethylcellulose sodium (Na CMC), ethylcellulose (EC), hydroxypropylcellulose (HPC), etc. Combination between different type and molecular weight (viscosity grade) of them enable obtaining variety of drug release profile from prepared systems.[27]

2. MATERIALS AND METHODS

2.1 Materials

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

2.2 Methods

2.3.1 Preparation of tablets from pellets via single-stage extrusion

The technological scheme for preparation of pellets via single-stage extrusion include weighting (electronic balance), sieving (0,5 mm mesh size sieve) and mixing (homogenizer - 10 min, 6 rpm) of API (theophylline) and excipients. 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).

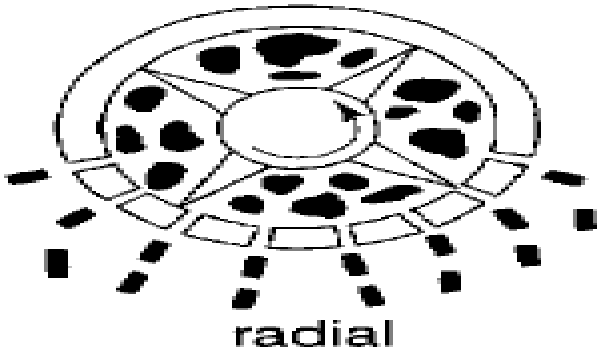

Fig. 1 Radial die of screw-feed extruder

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

The obtained extrudates/pellets undergo standard drying, classification and tabletting by 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%. The obtained tablets comply with the criteria for uniformity of mass (%RSD ≤5), uniformity of content, resistance to crushing and friability (≤1%).

Three formulations (E1-1-E3-1) according to the technology mentioned above were prepared (table 1). The first formulation (E1-1) consists of API theophylline and HPMC 4000 cP, the second formulation (E2-1) – theophylline with HPMC 80-120 cP and the third one (E3-1) – theophylline plus CMC Na 50-200 cP.

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

2.3.2 Preparation of tablets from pellets via two-stage extrusion

The technological scheme for preparation of pellets via two-stage extrusion include weighting (electronic balance) and mixing of obtained pellets from single-stage extrusion (pellets for E1-1-E3-1) with the needed amount of polymer (HPMC 4000 cP, HPMC 20-120 cP or CMC Na 50-200 cP) and wetting the mixture with 95% ethanol. The wetted mass was

re-extruded through radial screw-feed extruder (4M8Trix, Procept, Belgium) with die diameter 1,0 mm and 35 rpm feed rate of wet mass. The obtained extrudates/pellets undergo standard drying, classification and tabletting by compressed on Erweka AR401 single stroke tablets press with compression tooling for flat round tablets with diameter of 10 mm and average mass of one tablet – 300 mg ±5%. The obtained tablets comply with the criteria for uniformity of mass (%RSD≤5), uniformity of content, resistance to crushing and friability (≤1%).

Three formulations (E1-2-E3-2) according to the technology mentioned above were prepared (table 2). The first formulation (E1-2) consists of pellets from composition E1-1 with additionally adding of HPMC 80-120 cP, the second formulation (E2-2) – pellets E2-1 with CMC Na 50-200 cP and the third formulation (E3-2) – pellets E3-1 plus HPMC 4000 cP.

Table 2

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

2.3.3 Preparation of tablets from pellets via three-stage extrusion

The technological scheme for preparation of pellets via three-stage extrusion include weighting (electronic balance) and mixing of obtained pellets from two-stage extrusion (pellets for E1-2-E3-2) with the needed amount of polymer (HPMC 4000 cP, HPMC 20-120 cP or CMC Na 50-200 cP) and wetting the mixture with 95% ethanol. The wetted mass was then extruded through radial screw-feed extruder (4M8Trix, Procept, Belgium) with die diameter 1,2 mm and 35 rpm feed rate of wet mass. The obtained extrudates/pellets undergo standard drying, classification and tabletting by Erweka AR401 single stroke tablets press with compression tooling for flat round tablets with diameter of 13 mm and average mass of one tablet – 600 mg ±5%. The obtained tablets comply with the criteria for uniformity of mass (%RSD≤5), uniformity of content, resistance to crushing and friability (≤1%).

Three formulations (E1-3-E3-3) according to the technology mentioned above have been prepared (table 3). The first formulation (E1-3) consists of pellets from composition E1-2 with additionally adding of CMC Na 50-200 cP, the second formulation (E2-3) – pellets E2-2 with HPMC 4000 cP and the third formulation (E3-3) – pellets E3-2 plus HPMC 80-120 cP.

Table 3

Composition of tablets prepared from pellets via three-stage extrusion		
E1-3	**E2-3**	**E3-3**
Pellets from E1-2	Pellets from E2-2	Pellets from E3-2
CMC Na 50-200 cP	HPMC 4000 cP	HPMC 80-120 cP

2.3.4 In-vitro dissolution study of obtained formulations

In order to study the influence of type and viscosity grade of polymers and the stage of extrusion 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, and assay spectrophotometrically at λmax 273 nm. The amount of API (theophylline) dissolved (Q%), have 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 nine formulations (E1-1÷E3-1, E1-2÷E3-2 and E1-3÷E3-3) – tablets prepared from pellets via single-, two- and three-stage extrusion are shown in Table 4, 5 and 6.

Table 4

Amount theophylline released (Q%): tablets prepared from pellets via single-stage extrusion			
Time, h	**E1-1**	**E2-1**	**E3-1**
0	0	0	0
0,5	6,96	12,92	13,79
1	15,15	27,19	24,94
2	22,92	33,00	46,88
3	32,75	42,17	68,55
4	37,78	49,99	74,77
5	45,47	58,30	77,77
6	51,56	67,09	80,99
7	54,48	73,94	82,02
8	58,45	77,36	84,11
9	61,10	76,87	86,03
10	67,73	77,85	88.00

Table 5

Amount theophylline released (Q%): tablets prepared from pellets via two-stage extrusion			
Time, h	**E1-2**	**E2-2**	**E3-2**
0	0	0	0
0,5	6,44	5,62	3,97
1	11,08	8,83	6,75
2	16,33	13,43	12,61
3	20,58	22,93	27,26
4	26,84	35,44	54,65
5	32,02	47,02	60,58
6	34,69	56,29	63,81
7	37,78	64,47	64,86
8	43,37	66,33	65,49
9	45,79	68,58	67,78
10	49,38	70,24	69,42

Table 6

Amount theophylline released (Q%): tablets prepared from pellets via three-stage extrusion			
Time, h	**E1-3**	**E2-3**	**E3-3**
0	0	0	0
0,5	6,37	5,16	6,66
1	8,82	8,02	10,83
2	11,14	16,23	14,12
3	15,07	21,91	18,95
4	24,92	28,31	24,65

5	30,72	37,37	29,63
6	39,84	45,81	44,46
7	47,07	53,03	57,30
8	53,70	59,27	67,39
9	68,98	65,76	89,44
10	77,98	74,20	95,80

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.

For easier interpretation of data, results are applied in coordinate system (fig. 3,4 and 5): X-axis contains time in hours and Y-axis - % of API released.

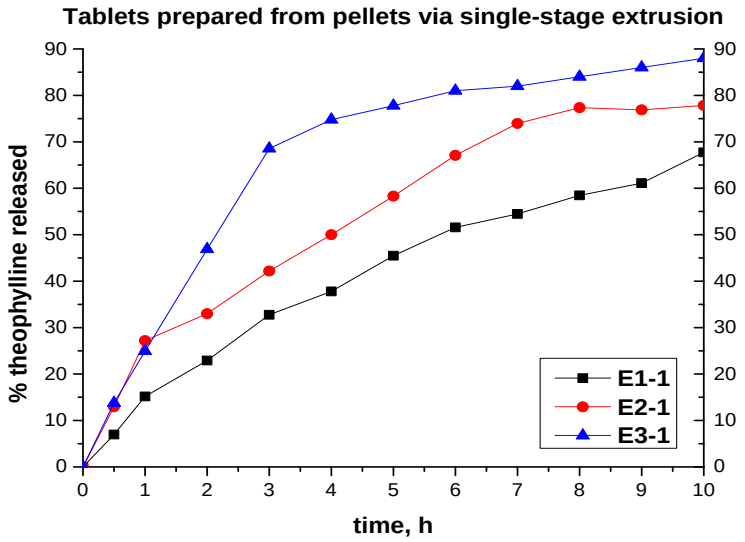

Fig. 3

As it can be predicted, the critical factors involved in drug release from tablets prepared from pellets via single-stage extrusion are type and viscosity grade of polymers. Unlike systems formed by non-biodegradable polymers, in which release is determined by diffusion of the drug through gel layer, obtaining first-order release kinetics, in systems with biodegradable polymers, like the present systems, based on CMC Na and HPMC with different viscosity grade, drug release is controlled by the entry of water into the matrix systems. This diffusion of water reflects in swelling of the polymers and matrix erosion and when these two processes are balanced, 0-order release kinetics can be obtained. Moreover the diffusivity of the drug through the matrix, the swelling of the polymer, and its dissolution rate can be changed by using CMC Na and HPMC with different viscosity grade.

All three formulations (E1-1-E3-1) satisfy the requirements for dissolution rate of theophylline (according to USP) – after 10 h, not less than 70% (Q) of the stated amount.

As it can be seen from fig. 3, increasing viscosity grade of HPMC (from HPMC with 80-120 cP to HPMC with 4000 cP) leads to increasing in swelling and decreasing in release rate of active pharmaceutical ingredient (API) – theophylline. That's why the release rate of E2-1 (HPMC 80-120 cP) is faster than E1-1 (HPMC 4000 cP). Between two polymers - HPMC and CMC Na, the last one swells less and exhibits faster release rate. Moreover with increasing of viscosity grade of HPMC the linearity of the curve increases, which is an indication that it's more likely to obtain zero-order kinetics release rate from tablets with HPMC with higher viscosity grade.

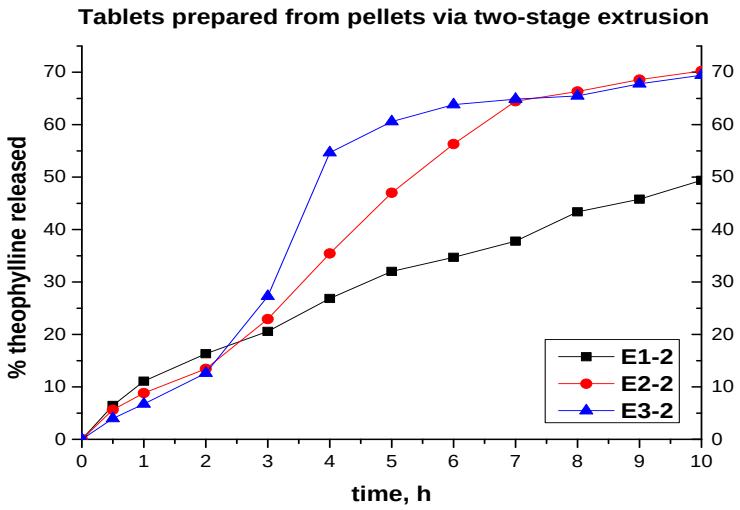

Fig. 4

The initial release of tablets prepared from pellets via two-stage extrusion (E1-2-E3-2) is pretty the same (12-16% for 2 h), but formulation E3-2 has really fast release rate after 3-rd hour (fig. 4). Because of the presence of CMC Na in formulations E2-2 and E3-2, the release of theophylline is satisfactory – more than 70% after 10 h. Formulation E1-2 has only HPMC, that's why % theophylline released after 10 h is unsatisfactory - below 50%.

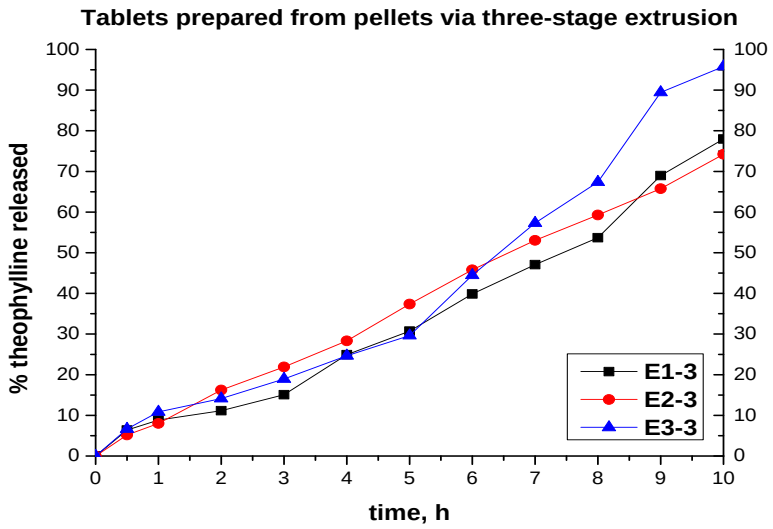

Fig. 5

Presence of all type of polymers in the three formulations of tablets prepared from pellets via three-stage extrusion (E1-3-E3-3) leads to similar release rate profiles (fig. 5).

The optimal formulation from chronopharmaceutical point of view is E3-3, because it has really slow initial rate (approximately 14% for the first 2 h) and then release complete (95% for 10 h). These systems (fig. 6), taken before bedtime, will deliver the API (theophylline) between midnight and the early morning hour when the asthma incidents are more probable to happen.

Fig. 6 Pictures of tablets prepared from pellets via three-stage extrusion, taken at 5 h of dissolution study: yellow – E1-3, red – E2-3 and green- E3-3.

3.2 Evaluation of the influence of the stage of extrusion on drug release from obtained formulation

The influence of the stage of extrusion (single-, two-, and three-stage extrusion) on drug release is presented in fig. 7÷9.

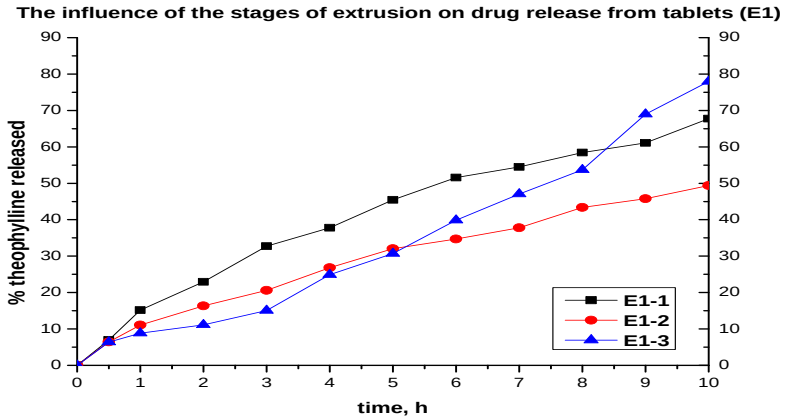

Fig. 7

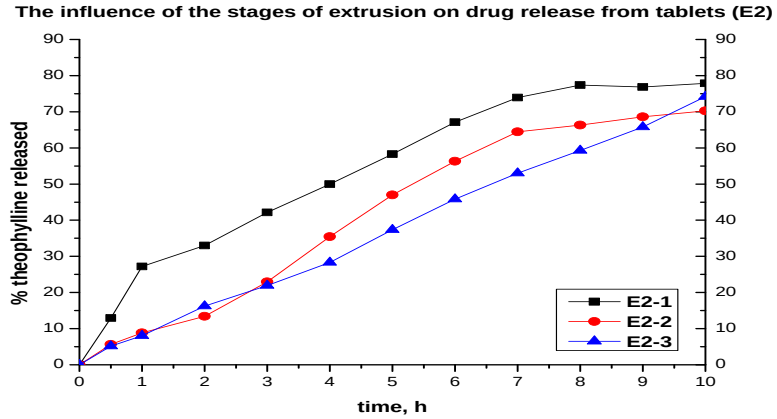

Fig. 8

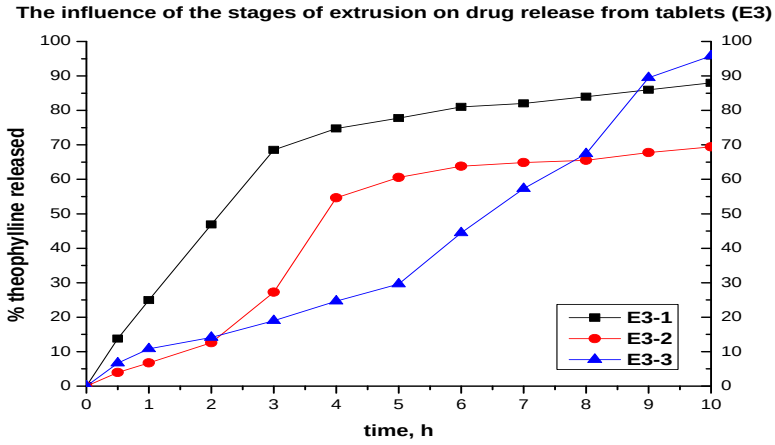

Fig. 9

As it can be seen from the drug release profiles (fig. 7÷9) 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 decreased. 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-stages extrusion, which leads to slowing of the drug release rate. In that case, three-stages extruded pellets act like three-layered coated pellets.

4. CONCLUSION

Data, obtained from the in-vitro dissolution study of nine different formulations tablets prepared by pellets via single- and multi-stages extrusion confirm the expectations about the influence of type of polymer and stage of extrusion on drug dissolution behavior. It was discovered that formulations with HPMC release slower that formulations with CMC Na. Moreover 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-stages extrusion, it can be conclude that the fastest is the release rate from single-extruded pellets and slowest – from three-stage extruded pellets. Among the all formulations, formulation E3-3 (tablet prepared from pellets via three-stage extrusion) exhibits the desired chronopharmaceutical release profile. This system is design, by taken before bedtime, to deliver API between midnight and early morning hours when asthma incidents are with higher frequency. This complies with the main principle of chronotherapy – synchronization of drug concentration to rhythms in disease activity. In conclusion, it can be summarized that tablets with theophylline prepared from pellets via multi-stage extrusion by utilization of different polymer blends and appropriate design could be a suitable system for prevention and treatment of asthma incidents.

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