

VALIDATION OF THE LABORATORY – SCALE TECHNOLOGICAL PROCESS PREPARATION OF A COLONIC RELEASE PHARMACEUTICAL SYSTEM WITH PH AND TIME-CONTROL

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Abstract

Validation of a manufacturing process is performed in order to ensure that the manufacturing process does what it purports to do. Pharmaceutical process validation guarantees the reliability and reproducibility of the manufacturing process.

The aim of this experimental work was to validate laboratory scale manufacturing process of a pharmaceutical system with pH and time-control colonic delivery system. The pharmaceutical system consists in minitables with indomethacin as model drug and sodium starch glycolate, as swelling agent, coated with a retardation layer that contains: an inner polimeric film insoluble and permeable (Eudragit RS) and an exterior polimeric enteric layer soluble pH – dependent (Eudragit L 55). The following steps of the technological process were validated: blending, tableting, coating with Eudragit RS and coating with Eudragit L 55. For each step of the pharmaceutical process the critical process parameters, responses with method of evaluation and acceptance criteria were established.

The results obtained on three laboratory scale batches performed in different days show that lab-scale technological processes are reliable and reproducible.

Rezumat

Validarea unui proces tehnologic este un program documentat științific. Acesta conferă un înalt grad de siguranță având în vedere că un anumit proces tehnologic va conduce în mod constant la un produs care întrunește atributele de calitate prestabilite.

Scopul acestei lucrări experimentale a fost validarea, la nivel de serie de laborator, a unui proces tehnologic de preparare a unui sistem farmaceutic cu cedarea colonică controlată de timp și pH. Sistemul farmaceutic constă în minitabele, cu indometacin ca substanță model și amidon glicolat de sodiu ca agent de umflare, acoperite cu un strat de retardare format din: un film polimeric interior insolubil dar permeabil (Eudragit RS) și un film polimeric exterior solubil dependent de pH (Eudragit L 55). Au fost validate următoarele etape ale procesului tehnologic: omogenizare, comprimare, acoperire cu Eudragit RS și acoperire cu Eudragit L 55. La fiecare etapă a procesului tehnologic s-au identificat parametrii critici, s-au stabilit parametrii controlați cu metodele de evaluare și criteriile de acceptare.

Rezultatele obținute pe trei serii de laborator preparate în zile diferite arată că procesul tehnologic este robust și reproductibil.

Keywords: colonic delivery; pharmaceutical process validation; Eudragit

Introduction

Although oral delivery has become a widely accepted route of administration for therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases (Chron's disease, ulcerative colitis, colorectal cancer and amebiasis) but also for its potential for the delivery of proteins and therapeutic peptides [1,2,3].

The development and the design of colon-specific drug formulations represent a technological challenge as these dosage forms must pass through the upper gastrointestinal (GI) tract in intact form, before delivering the drug to the colon. To achieve successful colonic delivery, a drug needs to be protected from absorption and /or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs [2,4,5]. Validation of a manufacturing process is ment to ensure that the manufacturing process does what it purports to do. Pharmaceutical process validation guarantees the reliability and reproducibility of the manufacturing process [6,7,8,9].

The aim of this experimental work was to validate the technological process of preparation, at laboratory scale, of a colonic delivery pharmaceutical system based on pH and time - control release device. The following steps of technological process were validated: powder blending, tableting, coating with Eudragit RS and coating with Eudragit L 55. For each step of the pharmaceutical process there were established the critical process parameters, the responses (with method of evaluation) and acceptance criteria.

Materials and methods

Materials. Indomethacin (Terapia SA, România), microcrystalline cellulose PH 102 (JRS Pharma, Germany), lactose monohydrate (Borculo, Netherlands), polyvinylpyrrolidone K25 (BASF, Germany), talcum (S&D Chemicals, UK), magnesium stearate (Union Derivan, Spain), Eudragit RS 30D, Eudragit L 5530D (Rohm Pharma, Germany), triethyl citrate (Merck, Germany), hydroxypropyl methylcellulose (Methocel E 15LV) (Colorcon, UK), titan dioxide (S&D Chemicals, UK), Simeticone (Colorcon, UK).

Apparatus. Tablet press EK-0 (Korsch, Germany), planetary mixer PRS (Erweka, Germany), fluid bed system Strea 1 (Aeromatic, Switzerland), UltraTurax (Janke and Kunkel, Germany), dissolution

apparatus PT-DT7 apparatus no. 1 (basket) (PharmaTest, Germany), spectrophotometer UV-Vis Jasco V530 (Jasco, Japan).

Minitablets preparation and characterization. The minitables were obtained via direct compressing using a Korsch EK 0 eccentric press equipped with die and punches of 5mm. The machine was adjusted in order to obtain minitables of 75 mg weight and hardness of minimum 6kg force. The tablets were evaluated for hardness, friability and mass uniformity using methods described in European Pharmacopoeia 5th Ed. The minitables were coated with polymeric films (Eudragit RS 30D, Eudragit L 55 30D), in a fluidized bed coating system (Strea 1, Aeromatic Filder).

In vitro release studies. Dissolution media: 900 ml 0.1N HCl solution (first 2 h) and phosphate buffer pH 6.8, (next 22h); rotation speed – 50rpm; temperature $37 \pm 0.5^{\circ}\text{C}$.

Results and discussion

The colonic delivery pharmaceutical system consists in minitables with indomethacin as model drug and sodium starch glycolate, as swelling agent, coated with a retardation layer that contains: an interior polymeric film insoluble but permeable (Eudragit RS) and an exterior polymeric enteric layer soluble pH – dependent (Eudragit L 55). The structure of the colonic release pharmaceutical system is presented in figure 1.

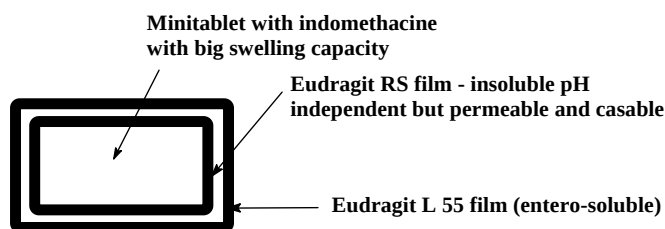


Figure 1

The structure of the colonic delivery pharmaceutical system

The optimum formula that was used in validation program was established using a central composite experimental design [10].

Results obtained after powder blending

For powder blend evaluation the following parameters were used: Carr index, Hausner ratio, time of flow and powder blend homogeneity. Results are presented in table I and table II respectively.

Table I
Results obtained on powder flow properties evaluation

No.	Batch	Untapped density (g/ml)	Tapped density (g/ml)	Carr Index	Hausner Ratio	Time of flow (seconds)
	Requirements	-	-	Max. 17	Max. 1,2	Max 30 sec
1	MCC001	0.466	0.5561	16.28	1.19	10.17
2	MCC002	0.462	0.5536	16.59	1.20	10.67
3	MCC003	0.480	0.5660	15.24	1.18	12.00

According to the results presented in table I the powders blend have very good flow properties, and there was found no significant difference among the three batches.

Table II
Results obtained on powder blend homogeneity evaluation

No.	Batch	Sample No.	Powder homogeneity			CV
			mg	%		
	Requirements		-	90-110%		CV< 5
1	MCC001	1	10.23	102.34	Mean	2.711
		2	10.44	104.4	10.1	
		3	9.943	99.43		
		4	9.784	97.84	SD	
		5	9.885	98.85	0.27	
2	MCC002	1	9.555	95.55	Mean	2.94
		2	10.14	101.4	10	
		3	10.35	103.5		
		4	9.973	99.73	SD	
		5	10.02	100.2	0.29	
3	MCC003	1	10.23	102.3	Mean	2.628
		2	10.52	105.2	10.1	
		3	10.03	100.3		
		4	9.984	99.84	SD	
		5	9.834	98.34	0.27	

According to the results presented in table II the powder blend homogeneity is very good, and there was found no significant difference among the three batches.

Results obtained in the tableting step

For compression process validation the following parameters were evaluated: uniformity of mass (table III and IV), friability (table V and VI), crushing strength (table V and VI), and content uniformity (table VII).

Table III

Results obtained on uniformity of mass (weight)
evaluation at the beginning of tableting process

No.	Batch	Individual value (mg)					Average mass (mg)	
	Requirements	50 mg 7.5%					50 mg $\pm$ 3%	
		Min. 46.2 mg					Min.	48.50mg
		Max. 53.7 mg					Max.	51.50mg
1	MCC001	48	50	51	50	Min.	50.0	+0.00
		50	50	51	50	48		
		51	50	50	50			
		48	50	51	50	Max.		
		49	50	50	51	51		
2	MCC002	50	48	50	52	Min.	50.1	+0.20
		51	50	51	51	48		
		50	49	49	51			
		51	51	50	48	Max.		
		52	50	48	50	52		
3	MCC003	50	51	52	50	Min.	50.6	+1.20
		51	51	52	52	47		
		51	50	50	49			
		47	50	51	48	Max.		
		51	51	52	53	53		

Table IV

Results obtained on uniformity of mass (weight)
evaluation at the end of tableting process

No.	Batch	Individual value (mg)					Average mass (mg)	
	Requirements	50 mg 7.5%					50 mg $\pm$ 3%	
		Min. 46.2 mg					Min.	48.50mg
		Max. 53.7 mg					Max.	51.50mg
1	MCC001	48	49	51	50	Min.	49.2	-1.70
		49	47	49	51	47		
		50	50	50	49			
		48	48	51	47	Max.		
		50	50	48	48	51		
2	MCC002	46	46	48	47	Min.	49.3	-1.40
		51	50	51	51	46		
		50	49	49	51			
		48	52	52	48	Max.		
		50	50	48	49	52		
3	MCC003	49	48	49	50	Min.	48.9	-2.20
		49	46	48	51	46		
		48	49	46	48			
		47	50	47	49	Max.		
		51	52	49	52	52		

Table V Results obtained on friability and crushing strength at the begining of tableting process					
No. Crt.	Batch	Friability	Crushing strength		
		(%)	(kg)		
	Requirements	Max. 0.2%	minim 6 kg		
1	MCC001	0	9	7.5	Mean
			8	8.5	8.1
			8	8	
			8	8.2	Min
			8	7.5	7.5
2	MCC002	0.098	8	7	Mean
			8	8	7.9
			7.5	8	
			8	8	Min
			8.5	8	7
3	MCC003	0.099	6	8	Mean
			8	6	7
			6	6	
			7.5	8	Min
			7.5	7	6

Table VI Results obtained on friability and crushing strength at the end of tableting process					
No. Crt.	Batch	Friability	Crushing strength		
		(%)	(kg)		
	Requirements	Max. 0.2%	minim 6 kg		
1	MCC001	0.000	8.0	7.0	Mean
			8.0	8.0	7.6
			8.5	7.7	
			7.0	7.0	Min
			7.0	7.5	7.0
2	MCC002	0.049	7.0	7.5	Mean
			8.0	6.0	7.4
			7.5	8.0	
			7.5	8.5	Min
			6.5	8.0	6.0
3	MCC003	0.145	6.5	7.0	Mean
			6.0	6.5	7
			6.0	6.0	
			7.7	7.0	Min
			7.0	7.5	6.0

Table VII
Results obtained on content uniformity determination

No. Crt.	Batch	Sample No.	Content uniformity			
			mg	%		CV
	Requirements		4.25- 5.75	85-115%	Mean/SD	CV< 5
1	MCC001	1	5.25	105.00	Mean 5.005 SD 0.178	3.56
		2	5.05	101.00		
		3	5.12	102.40		
		4	4.98	99.60		
		5	4.67	93.40		
		6	5.08	101.60		
		7	4.86	97.20		
		8	4.92	98.40		
		9	4.89	97.80		
		10	5.23	104.60		
2	MCC002	1	4.89	97.80	Mean 5.028 SD 0.148	2.96
		2	5.15	103.00		
		3	4.85	97.00		
		4	5.34	106.80		
		5	5.05	101.00		
		6	4.97	99.40		
		7	4.89	97.80		
		8	4.97	99.40		
		9	5.04	100.80		
		10	5.13	102.60		
3	MCC003	1	5.02	100.4	Mean 5.025 SD 0.155	3.08
		2	5.23	104.6		
		3	5.22	104.4		
		4	4.78	95.6		
		5	5.06	101.2		
		6	4.91	98.2		
		7	4.93	98.6		
		8	5.22	104.4		
		9	4.95	99		
		10	4.93	98.6		

The results from tablet preparation steps (table III - VII) show that the pharmaceutical process is robust and allows obtaining, in reproducible conditions, tablets with very good pharmacotechnical properties.

Results obtained during the validation of the coating process

There were two coating steps, first coating with an inlet polymeric film insoluble but permeable (Eudragit RS) and then coating with an outlet

polimeric enteric layer soluble pH – dependent (Eudragit L 55). The results obtained after coating are presented in fig 2, fig. 3 and table VIII.

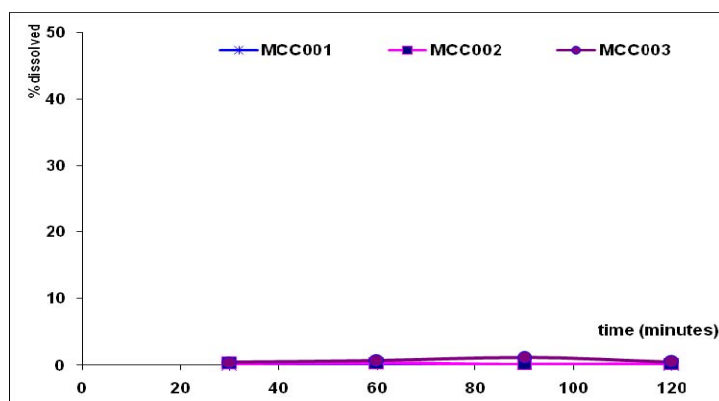


Figure 2
Indomethacin release form colonic delivery
pharmaceutical system in 0.1N HCl media

In 0.1N HCl media the amount of indomethacin released from all three validation batches is lower than 3%, and there was found no significant difference among the three validation batches.

Table VIII
Indomethacin release form colonic delivery
pharmaceutical system in phosphate buffer pH 6.8 media

Time (h)	Requirements	MCC001		MCC002		MCC003	
		Mean	SD	Mean	SD	Mean	SD
0		0.00	0.0	0.00	0.0	0.00	0.0
1	< 10 %	2.22	1.2	0.49	1.3	1.24	3.4
2	< 10 %	5.29	3.4	5.42	2.4	5.24	4.5
3	< 20 %	6.38	3.4	7.75	2.8	15.23	5.8
3.5		8.36	4.3	15.52	6.4	31.33	7.5
4		14.49	6.8	27.37	9.5	38.35	8.5
4.5		29.28	5.4	35.87	5.8	43.27	7.9
5		36.90	5.5	40.24	8.9	45.87	11.3
5.5		42.14	3.2	46.45	7.3	48.38	7.8
6	> 40 %	47.38	4.6	52.71	6.2	50.75	8.3
6.5		52.15	4.4	58.57	7.5	54.68	9.3
7		59.99	6.4	65.34	6.6	59.34	8.7
8		67.97	5.5	77.26	4.3	67.79	10.3
10		77.76	3.4	88.97	3.2	82.23	7.4
12	> 80 %	88.25	3.3	94.24	2.1	89.32	5.2
16		96.43	1.2	99.23	0.9	95.43	3.5
18		98.32	0.9	99.34	0.9	98.24	2.1
22		99.23	0.8	98.44	1.1	102.12	1.2

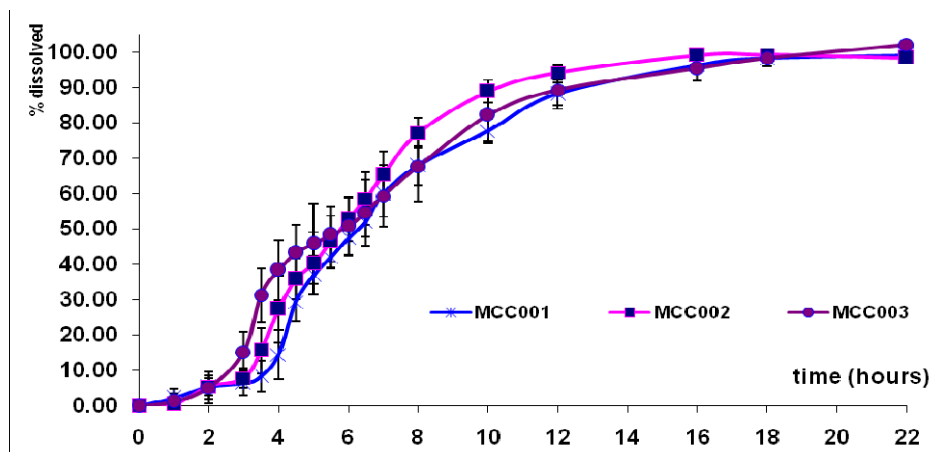


Figure 3
Indomethacin release from colonic delivery
pharmaceutical system in phosphate buffer pH 6.8 media

In phosphate buffer pH 6.8 media the amount of indomethacin released from all three validation batches in the first three hours was lower than 20%, after 6 hours was greater than 40% and after 12 hours was higher than 80%. The analysis of the release profile using similarity factor f_2 shows no significant difference among the three validation batches (table IX).

Table IX
Dissolution profile comparison in
phosphate buffer pH 6.8 media the validation batches

Validation Batches	f_2
MCC001 - MCC002	60.15
MCC001 - MCC003	51.95
MCC002 - MCC003	58.49

The results obtained at dissolution studies on the validation batch are very similar and in accordance to the parameters established during the colonic release system formulation and optimization.

Conclusions

The results obtained on all three validation batches of colonic release pharmaceutical system are very similar in all steps of the pharmaceutical technological process. Furthermore, all the results comply with the acceptance criteria established for each critical process parameter in the validation protocol.

In conclusion, the results obtained on three laboratory scale batches made in different days show that lab-scale technological processes are reliable and reproducible.

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