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Formulation development of theophylline in coated polymeric pellets for controlled oral drug delivery

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Abstract
This work is aimed at producing theophylline pellets for controlled oral drug delivery. Eight batches of theophylline pellets were prepared containing varying combinations (2.5 – 10% w/w) of sodium carboxymethyl cellulose, ethylcellulose and eudragit L-100 55. The flow properties of the pellets were determined and batches II and IV, which had the best flow were coated up to 30 – 60% using eudragit L-100. Sequential dissolution studies were carried out on the coated pellets in simulated gastric fluid (SGF), pH 1.2; simulated intestinal fluid (SIF), pH 6.8 and stimulated colonic fluid (SCF), pH 7.4. The dissolution data were subjected to kinetic treatment. The 30% coated pellets released uniform amounts of theophylline in the three media unlike the other batches. Though the coated pellets had the same super case-II transport mechanism of drug release, their release kinetics were different. The 30% coated batch-II pellets had the best controlled oral delivery of theophylline.

Keywords: Hydrophylic and hydrophobic matrices, theophylline, *in vitro* drug release kinetics, controlled release formulation, dissolution profile.

1. Introduction
Development of new drug molecules is expensive and time consuming. Controlled and sustained oral delivery of drugs reduce the challenges of frequent dosing, patients' need of privacy when the rectal route is preferred and provide opportunity for local treatment of gastrointestinal diseases. The development of controlled-release formulations continues to be a big success for the pharmaceutical industry. The success of any technology relies on the ease of its manufacturing process and reproducibility of desirable biopharmaceutical properties [1]. Several approaches have been developed in the design of controlled drug delivery systems and these include: reservoir systems with a rate controlled membrane, monolithic systems, laminated systems and chemical systems [2]. Several factors affect the successful design of controlled release products; these require careful consideration in the developmental process. These factors are: physicochemical properties of drug, biological process and routes of administration [3].
Though, there have been several publications discussing the delivery of theophylline in a sustained release formulation, its short half-life, and small dose, uniform absorption in the gastrointestinal tract and use in the treatment of chronic disease conditions have made it amenable for controlled release formulations. Theophylline is an effective bronchodilator used both as a prophylactic drug and to prevent acute exacerbation of asthma. Plasma concentration of theophylline above 15 µg/ml may produce effective bronchodilation in asthma. Controlled release formulations of theophylline will not only reduce dose frequency, but will also prevent possible incidence of toxicity [4].
Sodium carboxymethyl cellulose and ethyl cellulose are hydrophilic and hydrophobic polymers respectively, which have been applied in several aspects of controlled oral delivery either as coating materials, encapsulating agents or matrix formation [5]. The aim of this work therefore was to compare the combined effects of hydrophilic (sodium carboxymethyl cellulose) and hydrophobic (ethylcellulose or Eudragit L-100 55) matrices / coating level on the controlled oral delivery of theophylline.

2. Materials
Theophylline (BASF, India), eudragit L–100 55 (Eu) [Evonik Röhm GmbH, Germany], sodium carboxymethyl cellulose (SCMC) [Xuzhou Liyuan Chemical Co., Ltd, China], ethylcellulose (EC) [Dow Chemical Company, USA], lactose [Rich Pharma Chem, India], methanol [Usha Chemicals, India], ethanol [Virchand Fulchand & Bros., India], disodium hydrogen phosphate [Manas Chemicals, India].

3. Methods

3.1 Formulation of Theophylline Pellets

Eight batches of the theophylline pellets were formulated by the extruding the wet granulated mass through a 5-mL syringe. The hydrophobic matrix component was either a solution of eudragit® L-100 55 or ethylcellullose in 96% ethanol while the hydrophilic component was aqueous dispersion of SCMC. Lactose functioned as a bulking agent to achieve unit granule dose of 300 mg.

Appropriate quantities of theophylline and lactose were blended in a mortar and pestle prior to the introduction of the hydrophobic and hydrophilic components respectively. The mixture was triturated and kneaded to form a wet mass. Table1 shows the formulation composition. The wet mass was extruded through a 10-mL syringe and dried at 50 °C for 2 hrs. The pellets were screened through sieve 1.7 mm aperture and packaged in small cellophane materials

Table 1: Formula for the Preparation of Theophylline Pellets

Ingredient	Batches							
	I	II	III	IV	V	VI	VII	VIII
Theophylline	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100mg
SCMC	2.5%	5%	7.5%	10%	2.5%	5%	7.5%	10%
Eudragit L-100 55	2.5%	5%	7.5%	10%	-	-	-	-
Ethylcellulose	-	-	-	-	2.5%	5%	7.5%	10%
Lactose	185 mg	170 mg	155 mg	140 mg	185 mg	170 mg	155 mg	140 mg

3.2 Determination of Flow Properties

The following pellet properties were determined.

3.3 Flow rate and angle of repose of pellets

The funnel method was employed in the determination of flow rate and angle of repose. A 15 g quantity of the pellets from each batch was allowed to flow through a funnel of orifice diameter 1.2 cm at a distance of 15 cm from a cardboard paper basement. The time of flow, height and diameter of powder heap were recorded and the flow rate and angle of repose calculated [6]. Triplicate determinations were done.

$$Flow\ Rate = \frac{Weight\ of\ granulation\ (g)}{Flow\ time\ (s)} \qquad Eqt\ 1$$

$$Angle\ of\ Repose\ (Tan\ \theta) = \frac{Height\ of\ granulation\ heap}{Radius\ of\ heap} \qquad Eqt\ 2$$

3.4 Bulk and Tapped Densities

A 15 g quantity of each batch of granules was introduced in a 100 mL measuring cylinder and the granule height noted. It was later tapped 200 times from a height of 2.54 cm and the granulation height also noted [7]. Triplicate determinations were made and the bulk and tapped densities calculated according to the formula below:

$$Bulk\ Density = \frac{Weight\ of\ granulation\ (g)}{Bulk\ Volume\ of\ granulation\ (cm^3)} \qquad Eqt\ 3$$

$$Tapped\ Density = \frac{Weight\ of\ granulation\ (g)}{Tapped\ Volume\ of\ granulation\ (cm^3)} \qquad Eqt\ 4$$

3.5 Carr's Compressibility Index and Hausner's Quotient

Carr's compressibility index and Hausner's quotient [8] were calculated using the formulae below:

$$Compressibility\ Index = \frac{V_b - V_t}{V_b} \times 100 \qquad Eqt\ 5$$

$$Hausner's\ Quotient = \frac{V_b}{V_t} \qquad Eqt\ 6$$

Where V_b = Bulk volume, V_t = Tapped volume

3.6 Coating of Pellets

Since batches II and VI had the best flow properties, they were adjudged optimal and selected for subsequent coating. A 10%w/v solution of eudragit® L-100 in methanol was used to coat 300 mg of pellets from batches II & VI using an adjusted spray-coating pan method. Predetermined coating levels of 30% w/w and 60% w/w were achieved. The coated pellets were oven-dried to constant weight at 40 °C. [9]

3.7 *In Vitro* Drug Release Studies.

A sequential dissolution [10] of theophylline from the coated pellets was carried out in SGF (pH=1.2) for 2 h, SIF (pH=6.8) for 3 h and SCF (pH=7.4) for 3 hours. After dissolution in SGF, the medium was discarded and replaced with SIF. The same was the case with SCF. The drug release studies were performed in 500 ml of the appropriate medium maintained at 37±1 °C using the magnetic stirrer-beaker method at a rotation speed of 100 rpm. At predetermined time intervals, 5 mL samples were withdrawn and assayed spectrophotometrically (UNICO USA) at 340 nm (SGF) and 277nm (SIF and SCF). Meanwhile, fresh solution of the dissolution medium was replaced appropriately after each sampling.

3.8 Analysis of Data

The micromeritic properties of the pellets were compared to standard values while industrial implications of the flow rate results were evaluated. The data generated from dissolution studies were subjected to different in vitro release kinetic models [11] and compared using the FDA f_2 statistic model [12] whose formulae are represented below.

3.8.1 Zero Order Model

$C = k_0 t$

C = %Released, k_0 = Zero Order rate constant expressed in units of concentration/time (t)

3.8.2 First Order Model

$\text{Log } C_r = \text{Log} C_0 - k_1 t/2.303$

C_r = % Remaining, C_0 = Initial concentration of drug, k_1 = First order constant, t = Time

3.8.3 Higuchi's Square Root Law Model

$Q = k_H t^{1/2}$

Q = % Released, k_H = Constant reflecting design variables of the system, t = Time

3.8.4 Hixson-Crowell's Cube root Law Model

$[(100 – f)/100]^{1/3} = 1 - k_{HC}t$

f = % released, k_{HC} = rate constant, t = Time

3.8.5 Korsmeyer-Peppas Model

$M_t/M_\infty = kt^n$

M_t/M_∞=Fraction of drug released at time (t), k= Rate constant, '***n*-value**' is used to characterise different release mechanisms.

3.8.6 FDA (f_2) Statistic Model

$f_2 = 50 \bullet \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$

Where, n = number of time points (=16).

R_t and T_t = Dissolution data of the two dissolution profiles assessed. [11, 12]

4. Results

The flow properties of the uncoated pellets were evaluated and compared using the parameters listed in Table 2.

Table 2: Flow Properties of the Pellets

Batch	Micromeritic Parameter					
	BD(g/ml)	**TD(g/ml)**	**HQ**	**CI (%)**	**FR(g/sec)**	**Ø(^{0})**
I	0.56±0.01	0.63±0.002	1.13±0.004	17.40±0.04	4.20±0.001	21.8±0.02
II	**0.59±0.001**	**0.73±0.001**	**1.24±0.02**	**15.38±0.003**	**5.80±0.01**	**23.4±0.05**
III	0.50±0.01	0.63±0.01	1.30±0.01	3.90±0.02	4.57±0.001	26.7±0.07
IV	0.50±0.02	0.56±0.02	1.12±0.02	3.90±0.01	4.50±0.002	23.4±0.01
V	0.61±0.01	0.73±0.001	1.20±0.01	16.40±0.06	4.83±0.03	25.0±0.04
VI	**0.58±0.01**	**0.64±0.001**	**1.10±0.03**	**9.30±0.05**	**5.98±0.02**	**18.4±0.03**
VII	0.52±0.001	0.61±0.002	1.17±0.02	14.80±0.04	5.34±0.03	21.8±0.02
VIII	0.55±0.001	0.61±0.03	1.11±0.01	9.80±0.01	4.14±0.01	25.0±0.01

BD=Bulk Density, TD=Tapped Density, HQ=Hausner's Quotient, CI=Carr's Index, FR=Flow Rate and Ø=Angle of Repose

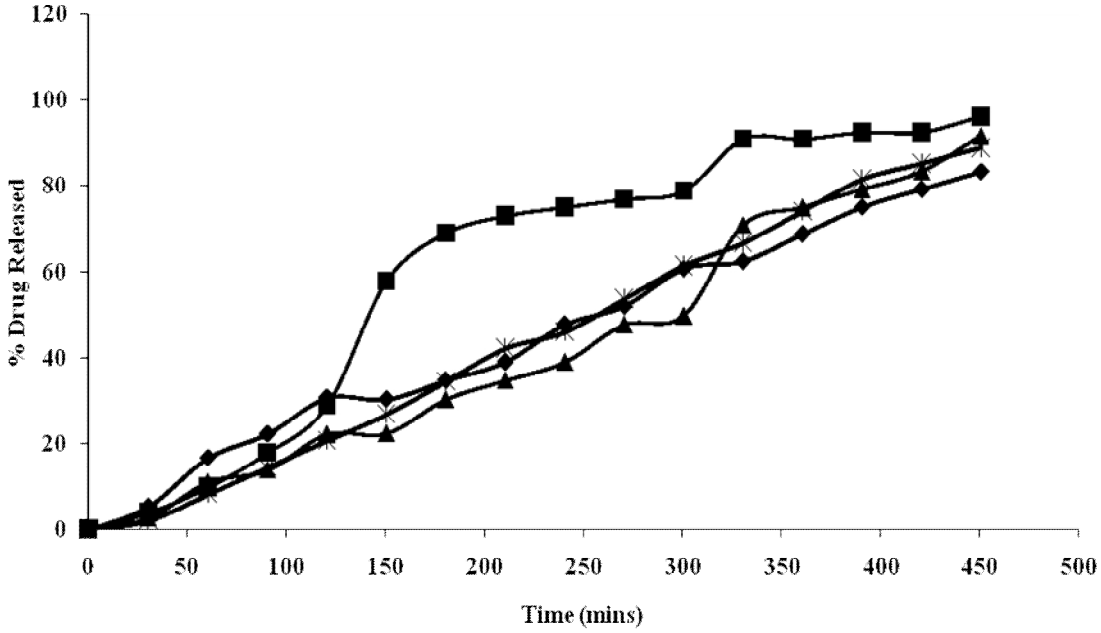

Figure 1: In Vitro Sequential Release of Theophyline from Eudragit L-100 55 Coated Pellets

5. Discussion

The differences in the bulk and tapped densities in batches I – VIII range from 0.06g/ml (≈0.1g/ml) to 0.14g/ml (≈0.1g/ml) with $p<0.05$. This means that there is no significant difference between the bulk and tapped densities. This is an indication that there are less interparticulate interactions between the powder (or pellet) particles. The result above shows that the pellets from the different batches would have good flow properties. [13] The compressibility indices between 5-15%, Hausner's ratios of less than 1.25 and angles of repose less than or close to 25º portrayed excellent flow properties. In addition, the higher flow rate values of batches II (5.8g/sec) and VI (5.98g/sec) informed their utility in the drug release studies. Kuksal *et al* [14] have previously prepared eudragit® and ethylcellulose-based granules with the angle of repose of less than 30º and excellent flow behavior. With a target capsule content weight of 300 mg, batches II and VI could

sustain the filling of 19 capsules per second, which is a very excellent feed rate for any capsule filling machine [15].

The release of theophylline from the coated pellets showed some interesting characteristics. The 30% coated batch-II pellets released almost equal amounts of theophylline – 30.77%, 30.09% and 26.65% in the SGF, SIF and SCF respectively with different rates of release of 0.26%/min, 0.17%/min and 0.15%/min in the three media. Reports have shown that there is no difference in the absorption of theophylline from the gastrum, small intestine and colon [16]. So, there will be no dose-related local toxicity or irritation at any site. But the 60% coated batch-II pellets released more than 40% of its theophylline content in the SCF and exhibited decreased release; 22.36% and 27.64% in the SGF and SIF respectively with release rates of 0.19%/min and 0.15%/min respectively. The decreased release rate was expected due to the increased coating thickness and moreover, this formula could be further optimized for targeted delivery to the colon. Furthermore, the half-life of absorption ($t_{1/2abs}$) of theophylline via the colon is prolonged when compared with that entering through the upper gastrointestinal tract [16]. Consequently, the drug stays longer in the colon for better controlled and prolonged release/absorption. The two release profiles complied with the zero order release kinetic model (R^2= 0.982 and 0.973 for 30% and 60% coated batch-II pellets). This means that the release of theophylline from these pellets is not concentration dependent [17].

Expectedly, the release of theophylline from coated batch-VI pellets containing ethylcellulose was retarded in SGF (29% and 20.82% release for 30% and 60% coated pellets respectively). This is attributed to the hydrophobicity of ethyl cellulose in the granule matrix. Although SCMC was a hydrophilic component of the matrix, the water-insolubility of ethylcellulose may have exerted a more palpable effect; thus retarding SGF diffusion through the matrix and subsequent dissolution of theophylline from the matrix. Liquid penetration into the matrix is the rate-controlling step in such systems, unless channeling agents are used [11]. As pH of dissolution medium (SIF) increased to 6.8, accelerated drug release took place (49 and 40.74% release for 30% and 60% coated batch-VI pellets respectively). On the other hand, reduced release was witnessed in SCF (17.43% and 29.14%, for 30% and 60% coated batch-VI pellets respectively).

The release kinetic of 30% coated batch VI pellets followed the first order release and Hixson Crowell Cube-root Law model (R^2=0.972 and 0.960 respectively). This implies that theophylline release from these pellets was more concentration-dependent, with moderate effects from the forces of erosion on the pellet surfaces. On the other hand, the observed zero order release kinetic (R^2= 0.991) for 60%-coated batch-VI pellets were more predominant than first order (R^2= 0.942) and Hixson Crowell (R^2= 0.936) models respectively. This also means that the release of theophylline from these pellets is not concentration dependent [17] and it is not affected by the forces of erosion on the pellet surfaces. [11]

To determine the mechanism of drug release, Korsmeyer-Peppas model was adopted. The 30% coated batches II and VI pellets had n-values of 0.924 and 1.188, while 60% coated batches II and VI had n-values of 1.210 and 1.303 respectively. The n-values >0.89 are indicative of super case-II transport. Therefore, the release of theophylline from these pellets was based on the relaxational behavior of the pellet matrices.

Finally, the dissolution profiles were compared using the similarity factor f_2. The release profiles for 30% coated batches II and VI pellets were found to be dissimilar with an f_2 value of 34.15 but the release profiles of 60%coated batches II and VI were similar with an f_2 value of 65.03. [12] The similarity in the release profiles of theophylline from 60% coated batches II & VI pellets also confirms their conformity to zero order kinetic model.

6. Conclusion

The 30% coated batch-II pellets had the best controlled oral delivery of theophylline. Though 60% coated batch-II pellets could be optimized for colonic delivery, it recorded similar release profile with 60% coated batch-VI pellets. Thus, they could be cross-substituted/compared. Therefore, coating of pellets modulated the release kinetics of theophylline from the coated batch-VI than batch-II pellets.

7. Reference

1. Yang L, Chu JS, Fix JA. Colon-specific drug delivery: new approaches and *in-vitro*/*in-vivo* evaluation. Int J Pharm 2002; 235:24.
2. Das GN, Das SK. Controlled-Release of oral dosage forms. Formulation, Fill & Finish, 2003, 10.
3. Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. J Controlled Release 2002; 79(1-3):7-27.
4. Chukwu A, Sabinus IO, Keneth U. Application of a polysaccharide derived from *Treculia Africana* as a sustained release hydrophilic matrix for theophylline hydrate tablet. Nig J Nat Prod and Med 1998; 2:37-41.
5. Sudhamani TK, Reddy NK, Ravi KVR, Revathi R, Ganesan V. Preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery. International Journal of Pharma Research and Development – Online 2010; 2(8):119-125.
6. Muazu J, Musa H, Bhatia PG. Evaluation of the glidant property of Fonio Starch. Research Journal of Applied Sciences, Engineering and Technology 2010; 2(2):149-152.
7. Hancock BC, Colvin JT, Mullarney MP, Zinchuk AV. The relative densities of pharmaceutical powders, blends, dry granulations, and immediate-release tablets. Pharmaceutical Technology 2003; 64–80.
8. Shah RB, Tawakkul MA, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. AAPS Pharm Sci Tech 2008; 9(1):250-258.
9. Eshra AG, Elkhodairy KA, Mortada SA, Nada AH. Preparation and evaluation of slow-release pan-coated indomethacin granules. J Microencapsul 1994; 11(3):271-278.
10. Fotaki N, Vertzoni M. Biorelevant dissolution methods and their applications in *in vitro-in vivo* correlations for oral formulations. The Open Drug Delivery Journal 2010; 4:2-13.
11. Uddin MB, Chowdhury JA, Azam KR, Islam MK. Investigation of the effects of different physicochemical parameters on *in vitro* release kinetics of theophylline from Eudragit NE 30 and Eudragit RS 30D matrix tablets. J Pharm Sci & Res 2010; 2(4):240-246
12. British Pharmacopoeia. Her Majesty's Stationery Office, Lodon, 2011.

13. Moore JW, Flanner HH. Mathematical comparison of curves with an emphasis on *in vitro* dissolution profiles. Pharm Tech 1996; 20(6):64-74.
14. Kuksal A, Ashok KT, Narendra KJ, Subheet J. Formulation and *in vitro*, *in vivo* evaluation of extended-release matrix tablet of Zidovudine: Influence of combination of hydrophilic and hydrophobic matrix Formers. AAPS Pharm Sci Tech 2006; 7:E1-9.
15. Heda PK, Muteba K, Augsburger LL. Comparison of the Formulation Requirements of Dosator and Dosing Disc Automatic Capsule Filling Machines. AAPS Pharm Sci 2002; 4(3):17.
16. Staib AH, Loew D, Harder S, Graul EH, Pfab R. Measurement of theophylline absorption from different regions of the gastro-intesinal tract using remote controlled drug delivery device. Eur J Clin Pharmacol 1986; 30:691-697.
17. Shoaib MH, Tazeen J, Merchant HA, Yousuf RI. Evaluation of Drug release kinetics from ibuprofen matrix tablets using HPMC. Pak J Pharm Sci 2006; 19(2):119-124.