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DISSOLUTION PROFILE AND DRUG RELEASE KINETICS OF THREE SPECIALLY FORMULATED THEOPHYLLINE ENTERIC COATED SOLID DOSAGE FORM: A COMPARATIVE STUDY

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***Abstract*— Dissolution profile and drug release from solid dosage form affected by many factors, and one of these factors is the type of the solid dosage form (i.e. tablet, capsule, pellets etc). This research attempt to determine the effect of the types of solid dosage form on dissolution profile, lag time, drug release rate and drug release kinetics. Three specially formulated enteric coated solid dosage form, i.e. enteric coated tablet (ECT), hard gelatin capsule filled with enteric coated granules (ECG) and enteric coated hard gelatin capsule (ECC) filled with drug in powder form, containing 100 mg of theophylline in each dose unit were prepared using almost the same inactive ingredients and coated with the same enteric coating formula. The results reveal a variation in dissolution profile and dissimilarity in release kinetics among the three dosage form. The dissolution behavior of ECG shows slower release rate with more consistency release pattern and ECT appear to be more similar to it, while ECC appear to be more like pulsatile release pattern.**

***Index Terms*—: Dissolution profile, Drug release, Solid dosage form, Enteric coating.**

I. INTRODUCTION

As advised by British National Formulary (BNF), patient with theophylline advised not to change the type of dosage form (or even the drug brand) because the dissolution profile and, accordingly, the rate of drug absorption was varied and can lead to a disproportionate change in serum-theophylline concentration and occurrence of adverse effects [1,2]. For this reason, it is crucial to compare the dissolution profile and drug release rate among different theophylline solid dosage form to help in choosing suitable alternative for each solid dosage form when there is a need to interchange [3]. Various factors effect on dissolution profile and drug release from solid dosage form including the physico-chemical properties of the drug, product formulation, type of dosage form, dose strength, dissolution testing apparatus and operation parameters [3,4]. To verify the effect of type of solid dosage form on rate and extent of drug release, most of the above mentioned factors should be excluded by formulation of the dosage form using same active (i.e. theophylline) and inactive ingredients, the same dose strength, and testing the prepared dosage form using same dissolution apparatus and parameters.

Oral solid dosage form such as tablets and capsules constitute about 58% of the total pharmaceutical dosage form in the drug markets worldwide [5]. Despite of the wide spread uses and the attractive properties provided by solid dosage form, there are a lot of drawbacks and troubles associated with the manufacturing, effectiveness, patient's tolerability and product stability. Many of the mentioned drawbacks could be overcome by enteric coating of the solid dosage form [6,7]. Enteric coating is, in particular, used to protect active substance(s) from degradation by the acidic gastric juice, improve tolerability of medicaments that irritating the stomach, modifying the release of drug and achieving targeted release [8]. Enteric coating, although mostly applied to tablets, can also be used to coat other solid formulations including capsules [7], and pellets. Different materials were used as film former for enteric coating varying in their physical and chemical properties as well as

differ in their protection effectiveness. One of earlier and most commonly used film former material is the Eudragit, a trademark of Rohm GmbH & Co. KG. Darmstadt, Germany, which is a pH dependent (pH 5.5 – 7) solubility polymer material [6].

Nowadays drug delivery researches are concerned in development of effective drug delivery systems with selectivity to release active ingredients in the target site(s) and with controlled drug release rate. The majority of drugs are mostly effective not only when made available near to absorption site(s) but also at a steady drug release rate [9,10]. Such goal can be achieve through enteric coating of the prepared dosage form [11]. Drug release rate, specially for modified release solid dosage form, is one of the important factor that determine the dissolution, absorption, bio-availability, the therapeutic activity and degree of effectiveness of solid dosage form [12,13].

Theophylline is belong to methyl xanthene and used in the treatment of asthma by acting as direct bronchodilator with some anti-inflammatory action in the airway as well [14]. Theophylline is slightly soluble in water, sparingly soluble in alcohol and chloroform and freely soluble in solutions of alkali hydroxides and in ammonia [2]. According to the biopharmaceutics classification system, theophylline belong to class I (highly soluble and highly permeable) [15]. The differences in the half-life and plasma concentration of theophylline are important because the toxic dose is close to the therapeutic dose (narrow therapeutic index). A plasma theophylline concentration of 10–20 mg/L (55–110 µmol/L) is required for satisfactory bronchodilation and the adverse effects can occur within the range 10–20 mg/L [1]. The narrow therapeutic index and the chronic uses of theophylline by the patients makes it very important to provide a dosage form with sturdy drug release profile. Reports have shown that there is no difference in the absorption of theophylline from major parts of gastro-intestinal tract [16], so, the absorption of theophylline is meanly depend on the drug release rate and the rate of absorption of released theophylline.

In this research the dissolution profile, lag time, drug release rate and drug release kinetics of three particularly formulated enteric coated solid dosage form, i.e. enteric coated tablet (ECT), hard gelatin capsule filled with enteric coated granules (ECG) and enteric coated hard gelatin capsule (ECC) filled with drug in powder form, containing 100 mg of theophylline were prepared using almost the same inactive ingredients and coated with the same enteric coating formula. Accordingly, the dissolution profile and drug release rate are only affected by the type of dosage form since other factors more or less were remained unchanged.

A. MATERIALS AND METHODS

1) Materials used for preparation of dosage form:

Anhydrous theophylline (Cipla, India), Microcrystalline cellulose (FMC corp., USA), Cross carmellose sodium, Magnesium stearate, Talc (Signet Chem. corp., India), Starch, anhydrous lactose (Rich Pharma Chem, India) and Hard gelatine capsule (type A) size #1 (Erawat pharma limited, India).

2) Materials used for preparation of enteric coating dispersion:

Eudragit L-100 powder (Rohm GmbH & Co., Germany), Polyethylene glycol 6000 (TNJ chemical industry, China), Titanium dioxide (HDC Technology Co., China), Acetone (Sigma –Aldrich), Colour No. 30, Talc powder (Signet Chem. corp., India) and Deionized water.

3) Experiment design:

A three theophylline dosage form, i.e. tablets, hard gelatin capsules and granules, were first prepared using the same ingredients and then coated with the same coating dispersion and the same coating method. The coating process was designed to produce enteric coating film almost with the same thickness for all the three dosage form under investigation to eliminate the affect of coating film thickness on dissolution profile and drug release rate as suggested by Noyes-Whitney rule [17]. The three prepared enteric dosage form were tested to determine the dissolution profile and lag time then the collected data were used to predict the drug release rate and release kinetics.

4) Preparation and evaluation of enteric coated tablets

The formulation of theophylline core tablet and the parameters of manufacturing were according to Prasanth *et. al.* 2012, with some modification according to Niazi 2009 [18,19], to make the formula suitable also for filling of hard gelatin capsules and preparation of enteric coated granules. A specific quantity of theophylline, microcrystalline cellulose, cross carmellose, starch and anhydrous lactose were mixed thoroughly for 5 minutes then, the core tablets were prepared by direct compression method using punch size 9 mm and claimed to have 100 mg theophylline each using a laboratory small scale single punch tablet compression machine (TDP-1.5 press, MINSHENG, China). Uniformity of dosage unit, disintegration time and drug content were tested according to USP30. Other manufacturer parameters for both core tablets and enteric coated tablets includes the weight variation, thickness, hardness, and friability, were also tested. The coating dispersion used was according to Mehdi 2015 [20], which is formulated originally for coating of hard gelatin capsules (using acetone instead of absolute ethanol) and find to be suitable for coating of tablet core and granules. For coating of tablets, spray coating pan were loaded with a preheated core tablets to 40˚C and the process was proceeded with a spraying rate 6 ml/min, inlet air temperature 55˚C, outlet air temperature 45˚C, coating nozzle diameter 1mm, a pan rotation speed of 40 rpm. The coating process repeated until getting a coating film of about 0.220 mm thickness measured using optical microscope (Olympus BX53) connected to digital processing unit operated by Genasis

version 7.1 software, then spread over a tray and oven dried at 55˚C for 2 hours.

5) Preparation of enteric coated hard gelatin capsules

Hard gelatin capsules (type A) size #1 were manually filled with 355 mg of the prepared powder mixture of a specific quantity of theophylline, microcrystalline cellulose, cross carmellose, starch and anhydrous lactose were mixed thoroughly for 5 minutes (an extra quantity of lactose was added to the formula to completely fill of capsule) and claimed to have 100 mg theophylline each. The weight variation, uniformity of dosage unit, drug content and disintegration time were tested according to USP30. The filled capsules were proceeded for enteric coating using spray coating pan with a spraying rate 2 ml/min, inlet air temperature 50˚C, outlet air temperature 40˚C, coating nozzle diameter 1mm, a pan rotation speed of 40 rpm. The coating process repeated until getting a coating film of about 0.220 mm thickness measured using optical microscope (Olympus BX53) connected to digital processing unit operated by Genasis version 7.1 software. To insure that the coating process was completed and perfect, the coated hard gelatine capsules were visually inspected to confirm formation of entirely continuous coating film with no breaks or cracks, then dried in oven for 4 hours at 45˚C.

6) Preparation of enteric coated granules

A wet granulation method was used to prepare a granules of 1mm size. A specific quantity of theophylline, microcrystalline cellulose, cross carmellose, starch and anhydrous lactose were mixed thoroughly for 5 minutes then a 5% starch paste was added and kneaded well until get a uniform wet mass. The wet mass was passed through a sieve No. 16, collect the granules and dry at 45 ˚C for 6 hours. Screen the dry granules through sieve No. 18 to get almost a uniform granule size of 1mm. A preheated granules to 40˚C was enteric coated using spray coating pan with a spraying rate 4 ml/min, inlet air temperature 55˚C, outlet air temperature 45˚C, coating nozzle diameter 1mm, a pan rotation speed of 30 rpm. The coating process repeated until getting a coating film of about 0.220 mm thickness measured using optical microscope (Olympus BX53) connected to digital processing unit operated by Genasis version 7.1 software. The coated granules were dried to constant weight at 45 ˚C in oven and sieved on a sifter to remove powder, smaller granules and agglomerates. The particle size distribution, uniformity of drug distribution and weight gain were evaluated. The coated granules was then manually filled in hard gelatin capsule size#1 and claimed to have 100mg theophylline each. The filled capsules was tested for uniformity of dosage unit and disintegration time according to USP30.

7) Comparing among the three dosage form

In an attempt to compare the dissolution profile, lag time and drug release behavior and rate, the three prepared enteric coated dosage form were tested according to USP 30 using the same testing condition and parameters. The lag time was calculated after the percent drug release became more than 5%. Dissolution test for the three enteric coated dosage form were carried out using USP apparatus II (Erweka DT 820 dissolution tester, Germany) test 1. In order to simulate the pH changes along with the gastro intestinal tract, dissolution media with pH 1.2 simulated gastric fluid (without pepsin) and phosphate buffer (pH 6.0) were sequentially used. The enteric coated dosage form was immersed in 900 ml simulated gastric fluid for 1 hour then removed and immersed in 900 ml of phosphate buffer (pH 6.0) for subsequent hours. Five ml of dissolution media was withdraw at predetermined time interval and fresh dissolution media was replaced. The withdrawn samples were analyzed at 271 nm using a UV spectrophotometer.

B. RESULTS

1) Enteric coated tablet

The prepared theophylline core tablets and enteric coated tablets were tested for their drug content, disintegration time, uniformity of dosage unit according to USP 30 in addition to percent weight gain and other manufacturing properties and the results were shown in Table 1. Other tests including dissolution time and dissolution profile were shown in Table 4.

2) Enteric coated hard gelatin capsules

The weight variation, uniformity of dosage unit and disintegration time of filled hard gelatin capsule were tested according to USP 30 and found to be within the pharmacopeia limits (Table 2). Other tests including lag time, dissolution time and dissolution profile were shown in Table 4.

3) Enteric coated granules

The uniformity of drug distribution, uniformity of dosage unit, and disintegration time were tested according to USP 30 and found to be within the pharmacopeia limits as shown in Table 3. Particle size distribution results revealed that 81.95 % of prepared pellets had average diameter of 1mm and overall prepared pellets were in diameter range 0.97-1.12 mm. Other tests including dissolution time and dissolution profile were shown in Table 4.

4) Lag time

According to USP30, the release of not more than 5% of the drug during the first step of dissolution test (using 0.1 N HCl as dissolution media) of enteric coated product is acceptable. For this reason and since the three dosage form tested shows a drug release of less than 5% at the first hour, the lag time was calculated after the end of first step plus the time needed by the dosage form to start drug release. The calculation of lag time revealed that ECC have a shorter lag time of 86 ± 0.5 min, with a dissolution behavior more as pulsatile release pattern, while ECG have the longer lag time of 89 ± 0.5 min. For ECT the lag time was 87 ± 0.5 min (Fig. 1). In general, no significant variation on lag time were observed among the three prepared dosage form.

Table 1: Evaluation of theophylline tablets

Test	Result
Drug content	100.2±0.86%
Tablet thickness (core)	5.38 ± 0.02mm
Tablet weight (core)	250mg ± 5%
Tablet weight (coated)	300 mg±5%
Percent weight gain	20 ± 2.6 %
Tablet Hardness (core)	7.4 kg/cm^2
Tablet friability (core)	0.306%
Disintegration time (core)	2.5 ± 0.5 min

Table 2: Evaluation of theophylline enteric coated hard gelatin capsules

Test	Result
Weight variation of uncoated capsule	348 – 356 mg
Weight of coated capsule	440 ± 3.8 mg
Percent weight gain	24 ± 3.25 %
Drug content	100.34 ±1.15 mg
Disintegration time (uncoated capsules)	4.5 ± 0.5 min
Disintegration time (coated capsules)	24.5 ± 0.5 min

Table 3. Evaluation of theophylline pellets

Test	Result
Uniformity of drug distribution	98 ± 1.34
Uniformity of dosage unit	99.2 ±1.55 mg
Disintegration time	4.0 ± 0.5 min
Percent weight gain	30± 3.88%

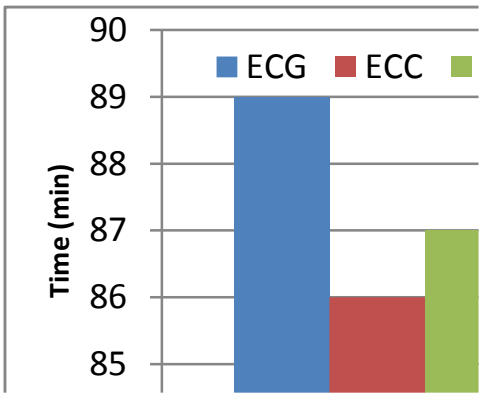


Fig. 1. The lag time for the three dosage form.

5) In-vitro dissolution test and drug release

The dissolution test for the three prepared enteric coated dosage form were performed at the same operation and testing conditions (Table 4) to study the drug release profile and to determine which enteric coated dosage form offers the best drug release behavior (Fig. 2)**.** The drug release rate for ECC was 0.576 % / min which is higher than other under investigation dosage form. For ECT and ECG the drug release rate was 0.492 % /min and 0.434 % /min respectively.

6) Similarity factor (f_2)

Based on model independent approach, similarity factor (f_2) was calculated to find out the degree of similarity in dissolution behavior among the three prepared enteric dosage form in which [9,10]:

$$f_2 = 50 * \log \{[1+ Q/n]^{-0.5} * 100. \quad (1)$$

The results reveals that dissolution behavior of ECT was more similar to dissolution behavior of ECG with $f_2 = 75.71$ and less similar to dissolution behavior of ECC with $f_2 = 71.06$. On the other hand, the dissolution behavior of ECC was dissimilar to ECG with $f_2 = 39.24$.

7) Drug release kinetics

The study of drug release kinetics involves Zero-order release model and First-order release model [17], as shown below:

Zero-order release model =

$$Q_t = Q_0 + K_0 t. \quad (2)$$

Where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, Q_0 = zero) and K_0 is the zero order release constant expressed in units of concentration/time.

First–order release model=

$$\text{Log } C = \log C_0 - K\, t/2.303. \quad (3)$$

Where K is first order rate constant expressed in units time^{-1}, C is drug concentration at time t, and C_0 is the initial drug concentration.

The results reveals that ECT and ECG tend to follow zero-order release kinetic (R = 0.963 and 0.981, respectively) which mean that the drug release is concentration independent. The release kinetic for ECC appear to be following first-order kinetic (R = 0.956) more than zero-order kinetic (R = 0.935) which implies that drug release from ECC was more concentration dependent with moderate effect of ability of dissolution media to solubilize and erode the coating film.

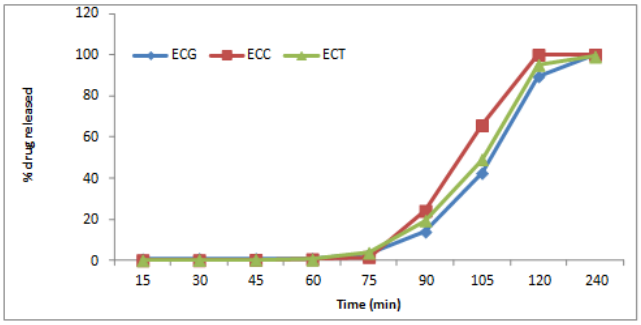
C. DISCUSSION

ECG shows higher percent weight gain per unit weight than the other two dosage form apparently due to larger surface area to be coated. Since the thickness of Eudragit L-100 coating film was the same for the three dosage form, so, the variation in lag time and drug release rate were assumed due to variation in nature of dosage form (including manufacturing process) and shape of the prepared dosage. ECC shows shorter lag time since the drug was existed as a fine powder which provides very large surface area of drug in contact with dissolution media and do not need for disintegration to be solubilize. For ECG and ECT which show a slightly longer lag time and slower drug release rate may be due to longer time needed for the drug to be completely in contact with dissolution media after eroding of coating film and disintegration of the compressed tablet and granules. The results of lag time and drug release rate directly affects on dissolution profile. The drug release kinetics of ECG and ECT follow zero-order kinetics which means that the drug release is controlled by the ability of

dissolution media to erode the coating film and dissolve the drug. The conformity in drug release kinetic between ECG and ECT was also confirmed by the similarity factor (f_2) and the resemblance in drug release profile.

Table 4. The dissolution time and drug release for the three enteric coated dosage form

Type of dosage form	Simulated Gastric fluid (min)				phosphate buffer (pH 6.0) (min)				
	15	30	45	60	75	90	105	120	240
ECG (n=12)	0.50 ±0.017	0.70 ±0.012	0.70 ±0.010	0.70 ±0.009	2.93 ±2.45	13.89 ±2.23	42.41 ±1.88	89.58 ±1.15	100.16 ±1.65
ECC (n=12)	0	0	0.20 ±0.011	0.53 ±0.017	1.56 ±2.65	24.11 ±1.97	65.74 ±2.83	100.12 ±2.55	100.25 ±0.98
ECT (n=12)	0	0.206 ±0.190	0.25 ±0.016	0.36 ±0.081	3.64 ±2.51	19.35 ±2.85	49.15 ±3.12	95.26 ±2.15	99.28 ±1.24



II. Conclusion

ECC shows higher drug release rate and faster drug dissolution than other two under investigation enteric coated dosage form and looks like a pulsatile release pattern. On the other hand, ECG shows the slowest drug release rate but with more consistency drug release. For a drug like theophylline with narrow therapeutic index and related to class I (highly soluble and highly permeable drug), ECG appears to be more effective and more safe dosage form than the other investigated dosage form. In addition to that, theophylline ECT can be consider as a good and acceptable alternative for the theophylline pellets to avoids the warning of BNF about the unsafely of altering theophylline dosage form.

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