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Formulation of Andrographis tablet from the antisolvent semi-purified Andrographis extract

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ABSTRACT

Andrographis paniculata extract, administered at 180 mg/day of andrographolide for 5 consecutive days, has been used to treat mild cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This research formulated 30 mg film-coated tablets of andrographolide, derived from a partially purified extract of Andrographis obtained using the antisolvent technique. The powdered extract was combined with microcrystalline cellulose and colloidal silicon dioxide to create core tablets through the wet granulation method. These core tablets were then film-coated. The Andrographis extract powder contained 40.27±1.18% andrographolide. The average weights of the core and film-coated tablets were 381.9 mg and 392.4 mg, respectively, each contained 31.0 of andrographolide. The average friability and hardness of the core tablets were 0.12±0.01% and 8.7±0.2 kg, respectively. The film-coated tablets completely disintegrated within 23 min, and the distribution of the extracted content in the tablet was uniform. The Andrographis tablets used in this study met all USP criteria.

Keywords: Andrographis; tablet; semi-purified; extraction; COVID-19

1. INTRODUCTION

Andrographis paniculata (Burm. f.) Wall. ex Nees, a member of the Acanthaceae family, is a well-known medicinal plant traditionally used to treat common cold. It exhibits a wide range of pharmacological activities, including antiviral, anti-HIV, antihepatitic, antimicrobial, antidiarrheal, anti-inflammatory, anticancer, antimalarial, immunostimulatory, antioxidant, antihyperglycemic, antihyperlipidemic, hepatoprotective, and cardiovascular effects (Hossain et al., 2014). Various extraction techniques have been employed for Andrographis extraction and purification, such as maceration, Soxhlet extraction, refluxing, sonication, microwave-assisted extraction, and supercritical carbon dioxide extraction, along with purification methods like partition and column chromatography (Pundarikakshudu et al., 2016). The whole Andrographis plant, when extracted with ethanol or methanol contains diterpenoids, with andrographolide the major compound, along with deoxyandrographolide, neoandrographolide, 14-deoxy11,12-didehydroandrographolide, 14-deoxy-14,15-didehydroandrographolide, 14-deoxy-14,15-didehydroandrographolide, 19-O-acetylanhydroandrographolide, and isoandrographolide (Chao & Lin, 2010).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), causes mild to moderate illness in most infected patients. However, 15% of cases become severe, and 5% progress to critical conditions, such as acute respiratory failure, particularly in patients with weakened immune systems (Aiyegbusi et al., 2021). The extract of

Andrographis paniculata exhibits anti-SARS-CoV-2 activity (Sa-ngiamsuntorn et al., 2021) and has been used to treat mild COVID-19 symptoms (Wanaratna et al., 2022), providing symptomatic relief for acute respiratory tract infections in adults and children (Hu et al., 2018). Mild COVID-19 patients who received a high dose of Andrographis extract (180 mg/day of andrographolide) for 5 consecutive days showed decreased levels of inflammatory cytokines IL2 and IL4, which are associated with COVID-19, with no cases of pneumonia reported among the treated patients (Intharuksa et al., 2022). Following the COVID-19 pandemic, the Thai FDA issued a "Drug Policy Committee's Announcement" titled 'The National List of Essential Medicines in Medicinal Herbs (No. 2) B.E. 2564 (2021)' (Thai Food and Drug Administration, n.d.), allowing the treatment of mild COVID-19 cases with 180 mg/day of andrographolide, either as a herbal powder or as an extract in Andrographis capsules or tablets. According to the Thai Herbal Pharmacopoeia (n.d.), the approved Andrographis herb must contain no less than 1% w/w of andrographolide (Thai Herbal Pharmacopoeia, n.d.). This implies that a COVID-19-infected patient should take a minimum required dose of 18 g of Andrographis herb per day. Alternatively, the patient can take 3 tablets, each containing 20 mg of andrographolide, 3 times a day. However, this regimen may lead to medication noncompliance. The film-coated tablet is a solid dosage form that can mask the bitter taste of Andrographis. Using Andrographis extract for drug preparation reduces the amount of the drug required per dose. However, the crude extract contains many constituents, some of which do not contribute to the drug's efficacy and may affect its stability (Thakur et al., 2011). Moreover, the physicochemical properties of the crude extract and the amount used depend on the manufacturing process (Qusaj et al., 2012). This study developed a green antisolvent technique to obtain a semi-purified Andrographis extract. The antisolvent precipitation process was utilized based on the poor solubility of compounds in aqueous media, with water used as an antisolvent to accelerate the precipitation of poorly water-soluble compounds (Viçosa et al., 2012). An Andrographis tablet containing 30 mg of andrographolide was formulated from the semi-purified extract to simplify the manufacturing process and enhance patient drug compliance.

2. MATERIALS AND METHODS

2.1 Materials

The aerial part of Andrographis powder was obtained from Kaew Mungkorn Phaesai (Ratchaburi, Thailand). Ethanol, methanol, Polyethylene Glycol 6000 (PEG 6000), acetonitrile (HPLC grade), and Polyvinylpyrrolidone K30 (PVP-K30) were purchase from Sigma Aldrich (Dorset, United Kingdom). Colloidal silicon dioxide (Aerosil®) was purchased from Evonik Industries (Essen, Germany). Sodium starch glycolate (Explotab®) was purchase from JRS Pharma (Rosenberg, Germany). Starch 1500® was obtained from Colorcon (Kim Seng Promenade, Singapore). Microcrystalline cellulose, hydroxypropyl methylcellulose (HPMC; E5LV and E15LV), lactose, magnesium stearate, titanium oxide, simethicone emulsion and talcum were purchased from P.C. drug center (Bangkok, Thailand). Brilliant blue and tartrazine were purchased from Phitsanuchemicals (Phitsanulok, Thailand). All other chemicals and solvents used were analytical grades.

2.2 Preparation of semi-purified Andrographis extract

The Andrographis powder was macerated 3 times with 95% ethanol. The resulting filtrates were combined and evaporated under reduced pressure. Distilled water was then added to the concentrated extract, acting as an anti-solvent to precipitate impurities during filtration. The filtrate was subsequently evaporated in a water bath to concentrate it further and then left at room temperature to allow for precipitation. The precipitant was collected by filtration, and the remaining supernatant was again evaporated in a water bath to concentrate it further. This was followed by second precipitation at room temperature. The combined precipitant was then dried in a hot air oven to obtain a semi-purified Andrographis extract. Finally, it was crushed using a mortar and pestle before being stored in a tightly sealed, light-protected container. The percentage of extraction yield was calculated using Equation 1.

$$\%\text{Extraction yield} = \frac{\text{The weight of extracted substance}}{\text{The weight of sample}} \times 100 \qquad (1)$$

2.3 Identification of crude and semi-purified Andrographis extracts by thin layer chromatography (TLC)

TLC chromatogram was performed using TLC-Silica gel 60 F254 (Merck, Darmstadt, Germany), with a mobile phase consisting of chloroform and methanol in a ratio of 85:15. The crude Andrographis extracts produced 3 spots, while semi-purified Andrographis extracts produced 4 spots. These were compared to a standard andrographolide. The chromatogram was visualized under UV light at 254 and 366 nm and then sprayed with Kedde's reagent.

2.4 Determination of andrographolide (AP1) and 14-deoxy-11,12 didehydroandrographolide (AP3) in the Andrographis tablets

The amounts of AP1 and AP3 were measured using a method described by Pholphana et al. (2013) with some modifications. HPLC analysis was conducted using the Agilent 1260 Infinity series. A Poroshell 120 EC C-18 column (3.0 x 150 mm, 2.7µm) from Agilent, equipped with a guard column was used. The mobile phase consisted of 28% acetonitrile in water, with a flow rate of 0.5 mL/min. The injection volume was 5 µL, and the detector was set to a wavelength of 205 nm. Standard curves for AP1 and AP3 were prepared. The amount of AP1 was determined in the extract, core tablet, and film-coated tablet, while AP3 was quantified only in the crude and semi-purified extract.

2.5 Evaluation of loss on drying of semi-purified Andrographis extract

The moisture content of the semi-purified Andrographis extract was determined using a moisture analyzer (MS-70, A&D Company, Tokyo, Japan). An aluminum pan was placed on the analyzer's integrated scale and zeroed. A 1 g sample of the extract was then added to the pan to initiate the drying procedure. The standard loss-on-drying method was followed, with the sample dried at 105 °C for 30 min.

The analyzer recorded the initial weight of the moist sample and continuously monitored its weight throughout the drying period. The process was completed when the weight loss stabilized at a preset value. This procedure was repeated 3 times and the average percentage of loss on drying was calculated.

2.6 Evaluation of particle size of semi-purified Andrographis extract

The particle size of the semi-purified Andrographis extract powder was assessed using a light microscope (Leica DM 100, Wetzlar, Germany) equipped with an ocular micrometer and a stage micrometer. Particle size was determined by measuring the Feret's diameter. The mean particle size and its standard deviation were reported

2.7 Preparation of Andrographis core tablets

For the preparation of 40% partially purified, mixed andrographolide extract, the semi-purified Andrographis extract was dissolved in ethanol and then combined with a 9:1 mixture of microcrystalline cellulose and Aerosil®. The mixture was dried in a hot air oven to produce a mixed Andrographis extract powder containing 40% andrographolide. The formulation for the 30 mg Andrographis tablet is presented in Table 1. The mixed Andrographis extract was blended with lactose, Starch 1500®, and microcrystalline cellulose in a wet mixer for approximately 15 min. A solution of PVP-K30 in purified water was gradually added to this blend to form a wet mass. This wet mass was then sieved using an oscillating granulator fitted with a No. 12-16 sieve. The granules were dried in a hot air oven at 50 °C until the moisture content was less than 5%. The dried granules were further sieved using a No. 18 sieve on an oscillating granulator. Finally, Explotab® and magnesium stearate were mixed with the dried granules, and the mixture was processed into 380 mg core tablets using a rotary tableting machine.

Table 1. The master formula for 30 mg Andrographis core tablet

Andrographis core tablet	Amount
40% mixed partial-purify andrographolide extract (Equivalent to Andrographolide 30 mg)	75 mg
Lactose	55 mg
Starch 1500®	55 mg
PVP-K30	3.8 mg
Water	60 mg
Explotab®	16 mg
Magnesium stearate	3.8 mg
Microcrystalline cellulose (Adjust to keep final tablet weight to 380 mg)	186.4 mg

2.8 Evaluation of friability and hardness of core tablets

The friability and hardness of the core tablets were evaluated according to USP 2021 guidelines. Friability was determined using 17 randomly selected core tablets, totaling approximately 6.5 g in weight (381.9 mg × 17 tablets). These tablets were initially weighed together and then placed in a Friabilator machine (HMKTablet 1601, Roche Model, Aimsizer scientific, Dandong, China), which rotated at 25±1 rpm for 100 revolutions. Afterward, the core tablets were weighed again, and the percentage of friability was calculated using Equation 2. The hardness of 10 randomly selected core tablets was measured using a Stokes-Monsanto hardness tester (Erweka GmbH, Heusenstamm, Germany), recording the maximum force required to break a tablet.

$$\%\text{Friability} = \frac{\text{Initial weight } (W_1) - \text{Final weight } (W_2)}{\text{Initial weight } (W_1)} \times 100 \quad (2)$$

2.9 Preparation of Andrographis film-coated tablet

The composition of the film coating solution is presented in Table 2. Briefly, isopropyl alcohol was mixed with purified water. HPMC E15LV and HPMC E5LV were then dissolved in this mixture, followed by the addition of PEG 6000. Subsequently, simethicone emulsion, talcum, titanium oxide, brilliant blue, and tartrazine were added and thoroughly mixed using a magnetic stirrer. This solution was used to coat the Andrographis core tablets with a coating machine. After coating, the percentage of weight gain in the tablets was calculated using Equation 3.

$$\%\text{Weight gain} = \frac{\text{Final weight } (W_2) - \text{Initial weight } (W_1)}{\text{Initial weight } (W_1)} \times 100 \quad (3)$$

Table 2. Composition of the film-coating solution

Film coating solution	Amount
HPMC E15LV	3.2 mg
HPMC E5LV	3.2 mg
PEG 6000	1.2 mg
Talcum	1.596 mg
Titanium oxide	0.6 mg
Brilliant blue	0.024 mg
Tartrazine	0.120 mg
30% Simethicone emulsion	0.2 mg
Isopropyl alcohol	0.055 mL
Water	0.055 mL

2.10 Evaluation of content uniformity

Ten tablets each of the core and film-coated Andrographis tablets were weighed, and their average weight was determined. These tablets were then crushed using a mortar and pestle. The resulting powder was dissolved in 10 mL of water, followed by the addition of 75 mL of methanol. Additional methanol was added to bring the total volume to 100 ml. This mixture was filtered through Whatman filter paper No. 5. The sample was then appropriately diluted with methanol and analyzed by HPLC. The content uniformity of both the core and coated tablets was evaluated using the methods outlined in USP 2021.

2.11 Evaluation of disintegration time

The disintegration time of the film-coated tablets was measured following the methods outlined in USP 2021. A rigid basket-rack apparatus (Nottingham, United Kingdom) was employed. Six film-coated tablets were tested simultaneously for accuracy over a period of 1 h. Each tablet was placed in a vessel (without a disk) and oscillated at 30 cycles/min. The dissolution medium, consisting of 900 mL of 0.01 M hydrochloric acid with 0.2% w/v sodium lauryl sulfate at pH 6.8, was maintained at 37±2 °C. Disintegration time was recorded when all fragments of the tablet had passed through the mesh at the bottom of the vessel. All measurement were performed in triplicate and results were reported as the mean±SD.

2.12 Evaluation of dissolution

An *in-vitro* dissolution study of the film-coated tablets was conducted following USP 2021 guidelines, using dissolution apparatus II (paddle) (Nottingham, United Kingdom). The dissolution medium, consisting of 900 mL of 0.01 M hydrochloric acid with 0.2% w/v sodium lauryl sulfate at pH 6.8, was maintained at 37±2 °C with a paddle speed of 100 rpm. At predetermined time points (15, 25, 35, 45, 60, 75, and 90 min), 10 mL samples were withdrawn and replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The amount of AP3 dissolved from the film-coated tablets was measured using HPLC. The phosphate buffer solution (PBS) pH 6.8 was used as a control (Charupant et al., 2017; Suriyaamporn et al., 2023).

2.13 Statistical analysis

The research was conducted in triplicate, and results were reported as averages with corresponding standard deviations (SD). The two-sided independent *t*-test was used to compared two groups, with statistical significance determined for *p*-values below 0.05. SPSS® software version 19 (SPSS Inc., Chicago, IL) was utilized for statistical analysis.

3. RESULTS AND DISCUSSION

3.1 Preparation and evaluation of semi-purified Andrographis extract

The crude Andrographis extract was a green sticky paste, with an extraction yield 12.11±0.68% based on the dry plant weight. The extraction yields of AP1 and AP3 were 19.78±0.84% and 5.78±0.11%, respectively, based on the dry extract weight. The sticky nature of the crude extract impacted the mixing process during manufacturing and the uniformity of the tablet content. To address this, the antisolvent technique was employed by adding water to precipitate nonpolar impurities such as chlorophyll. The supernatant was evaporated to concentrate andrographolide and its derivatives, and then left to stand overnight for precipitation. The semi-purified extract was dried and crushed into a light yellow-brown powder, with an extraction yield 2.12±0.18% based on dry plant weight, as shown in Table 3.

The semi-purified extract was qualitatively assessed using TLC, sprayed it with Kedde's reagent, and compared with the crude extract (Figure 1). The TLC chromatograms of the crude and semi-purified extracts were identical, except that the semi-purified extract did not show green chlorophyll spots and yellow carotene spots. The range of retention factor (Rf) of spots on 1-8 lanes of chromatogram C is shown in Table 4. The amounts of AP1 and AP3 in the semi-purified extract were 62.19±2.22% and 8.16±0.22% w/w, respectively based on the dry extract weight. The andrographolide content was calculated relative to the total lactones, which includes AP1, AP3, neoandrographolide (AP4), and 14-deoxyandrographolide (AP6). The amounts of AP3 in the crude extract and semi-purified extract were 8.82% and 11.35%, respectively (Note: No peaks of AP4 and AP6 were observed in the HPLC chromatogram of the semi-purified extract). The peaks were identified in the HPLC chromatogram of the Andrographis extract in the study by Pholphana et al. (2013). These results complied with the criteria outlined in the Notification of the Ministry of Industry (No. 5341) B.E. 2562 (2019), published in Government Gazette, Volume 136, special part 186d, which specified that powdered Andrographis extract should contain at least 6% w/w andrographolide and no more than 15% of the total diterpene lactones of 14-deoxy-11,12-didehydroandrographolide. The percentage loss on drying of the semi-purified extract was 3.35±0.13%, and the particle size ranged from 2.56 to 15.38 μm, with approximately 60% of the particles falling within the range 2.56 to 7.69 μm.

Table 3. The % extraction yield of Andrographis from crude and semi-purified extracts

% Extraction yield	Crude extract (%w/w)	Semi-purified extract (%w/w)
Total*	12.11±0.68%	2.12±0.18%
AP1**	19.78±0.84%	62.19±2.22%
AP3**	5.78±0.11%	8.16±0.22%

Note. *Based on the dry plant weight; **based on the dry extract weight.

Table 4. The rage of retention factor (Rf) of spots on 2-8 lanes of chromatogram C

Position of spots	Range of retention factor (Rf)
a	0.75 – 0.77
Andrographolide (b of lane 1)	0.63
b	0.60 – 0.63
c	0.35 – 0.37
d	0.21 – 0.22

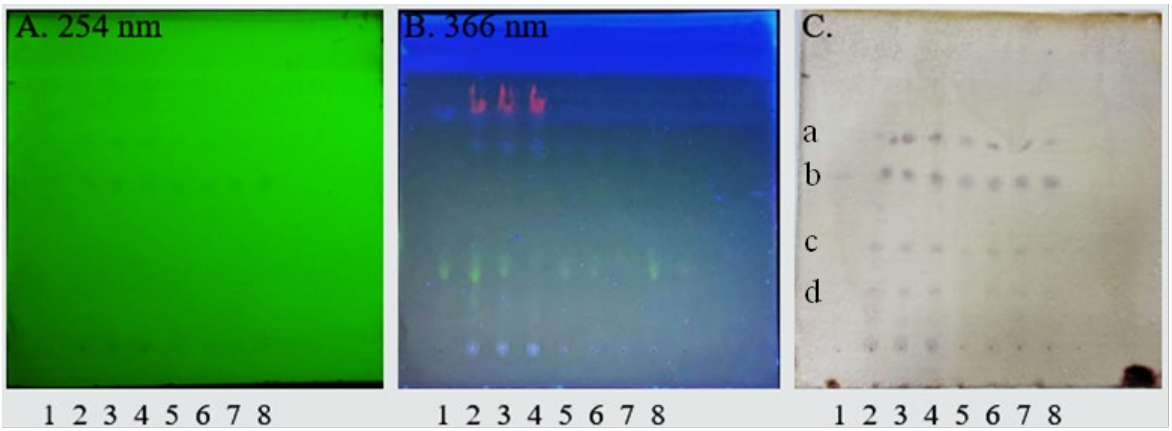

Figure 1. TLC chromatograms of standard andrographolide (spot 1), crude Andrographis extract (spot 2, 3, 4) and semi-purified Andrographis extract (spot 5, 6, 7, 8), visualized at A. 254 nm, B. 366 nm and C. Detection after spraying with Kedde's reagent

3.2 Preparation and evaluation of Andrographis core and film-coated tablets

Andrographolide has poor water solubility, which affects its bioavailability, making tablet a suitable major dosage form (Guo et al., 2012). The thermodynamic stability of the crystalline form of the drug is crucial. The amorphous state of the drug had high energy and mobility, rendering its less thermodynamically stable. Solid dispersion can enhance the solubility of a poorly water-soluble drug but may lead to recrystallization, thereby affecting the drug's solubility. To address this, a hydrophilic polymer was employed to improve the stability of the amorphous drug (Chaudhari et al., 2020). Microcrystalline cellulose and Aerosil® (colloidal silicon dioxide) were selected as carriers. Microcrystalline cellulose was selected due to its extensive use in the pharmaceutical industry, ready availability, high stability, and reported ability to enhance the solubility of poorly soluble drugs (Kostelanská et al., 2022). Colloidal silicon dioxide was selected as a nonporous carrier for its effectiveness in formulating poorly soluble drugs, leading to increased dissolution rates and higher bioavailability (Bhagwat & D'Souza, 2012).

The semi-purified extract facilitated the manufacturing process as it was a fine powder, making it easy to handle and measure. The semi-purified extract solution was physically mixed with microcrystalline cellulose and Aerosil® in a 9:1 ratio, the resulting dried mixed Andrographis extract powder contained 40.27±1.18% andrographolide. The physical appearances of the core and film-coated tablets are shown in Figure 2. The film-coated tablets had a smoother and more matte texture compared to the core tablets. Advantages of film-coated tablets over commercial products include enhanced aesthetic appeal, flavor masking, and reduced moisture absorption.

The average weight of the core tablets was 381.9 mg, with each tablet containing 31.04±0.31 mg of andrographolide (equivalent to 103.46±1.03% of the labeled amount). The friability and hardness of the core tablet were 0.12±0.01% and 8.7±0.2 kg, respectively. The core tablet met USP criteria for friability, where the maximum mean weight loss should not exceed 1.0% and there should be no broken tablets. The hardness also fell within the accepted range of 7–9 kg. The average weight of the film-coated tablets was 392.4 mg, with each tablet containing 30.96±0.47 mg of andrographolide (equivalent to 103.21±1.56% of the labeled amount). The film-coated tablets showed a 2.56% weight gain after coating. Both the core and film-coated tablets met USP criteria for content uniformity, with no significant differences in weights and drug contents between the two tablet types.

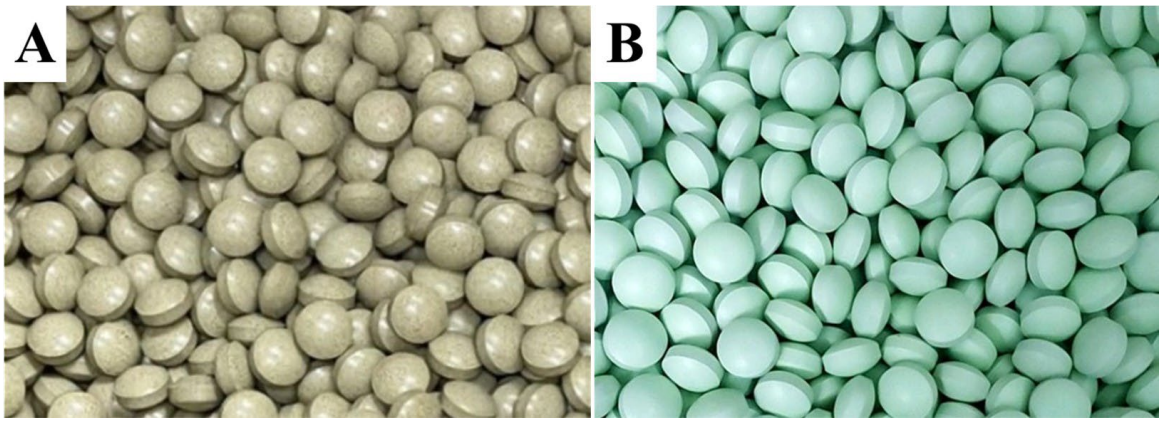

Figure 2. The physical appearances of the (A) core and (B) film-coated tablets

3.3 Disintegration time and dissolution of Andrographis film-coated tablets

The average disintegration time of the six coated tablets was 23.33±2.06 min, with all tablets disintegrating within the 30-min limit specified by USP 2021. This performance is attributed to the inclusion of Explotab®, a highly disintegrant commonly used in various tablet formulations (Muñoz et al., 1998). The dissolution profiles of the coated tablets at various time points were as follows: 22.56±2.35% at 15 min, 42.18±3.36% at 25 min, 53.13±1.91% at 35 min, 57.71±2.36% at 45 min, 62.75±2.57% at 60 min, 65.72±3.04% at 75 min, and 67.11±3.36% at 90 min (Figure 3). These results indicate that the dissolution of andrographolide from the film-coated tablets was not optimal. To improve dissolution, adjustments to the tablet formula may be necessary, such as adding an intra-granulation disintegrant or surfactant, or exploring internal solid dispersion techniques during preparation.

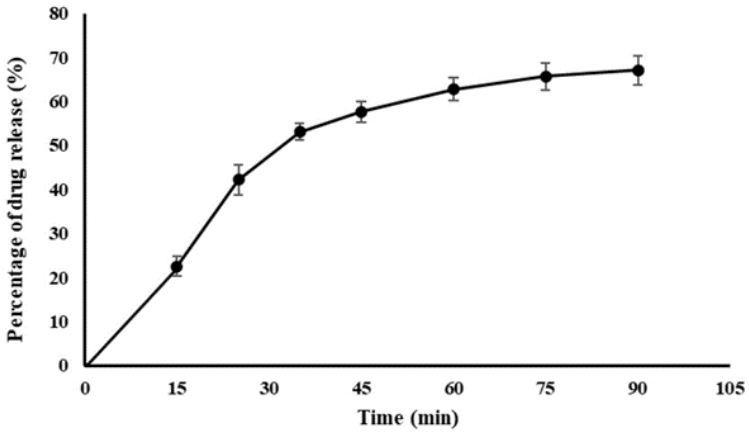

Figure 3. *In- vitro* dissolution profile of Andrographis film-coated tablet

4. CONCLUSION

The development of herbal medicines for modern use faces challenges, primarily due to the variability of raw materials and the lack of standardized quantification method. In this study, we employed an antisolvent technique using water to purify Andrographis extract, a process that is eco-friendly, simple and accessible for local industries. The resulting semi-purified extract, in powder form, facilitated the manufacturing process compared to the crude extract.

Our formulated Andrographis tablet, utilizing this semi-purified extract, met acceptance criteria for content uniformity, friability, hardness, assay, and disintegration. However, it did not fully meet the dissolution criteria. No standardized protocols for dissolution of Andrographis tablet are currently available. Formula adjustments may be required to obtain optimal drug dissolution. To enhance dissolution and drug bioavailability, future modification might include adjusting the disintegrant ratio, incorporating surfactants, or exploring new dispersion techniques.

The film-coated tablets offer advantages over commercial products, such as improved aesthetic appeal, flavor masking, and reduced moisture absorption. Future research should focus on evaluating the therapeutic potential, safety, and patient compliance of Andrographis film-coated tablets for individuals affected by COVID-19.

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