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Development and Evaluation of Enteric Coated Herbal Drug Delivery System for Treatment of Asthma

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ABSTRACT: *Adhatoda Vasica is a plant believed to have several therapeutic effects including anti-asthmatic properties. The purpose of study was to develop its tablet formulation by direct compression technology for prevention of episodic attack of asthma in early morning. To achieve the objective, formulations containing core immediate release Adhatoda Vasica tablets were prepared by direct compression method using different concentrations (2.5 – 7.5%w/w) of superdisintegrant cross caramellose sodium. Each formulation was characterized in terms of hardness, friability, drug content and in-vitro disintegration time. On the basis of disintegration profile, the selected best formulation was coated with ethyl cellulose as inner layer and Eudragit S100 as outer enteric-coating layer which retards the drug release in stomach but releases the drug immediately in the intestinal pH. The optimized enteric-coated formulation CF6 containing 2.5% w/w of Eudragit S 100 and 25% w/w of ethyl cellulose as coating system inhibited the release of the drug in 0.1 N HCl, and whereas 91.46% of drug was released in the intestinal medium at the end of 10 hrs. Thus, dissolution profiles indicated that CF6 tablet may be better alternative in the treatment of nocturnal asthma which overcomes the problems of conventional forms. The results obtained revealed that developed vasaka formulation exhibited a promising role in release of drug after a lag time which is essential for chronotherapeutic delivery.*

KEY WORDS: *Adhatoda Vasica, asthma, chronotherapy, direct compression, enteric coating.*

I. INTRODUCTION

Bronchial asthma is a disease characterized by increased responsiveness of the trachea, bronchi and bronchioles to various stimuli and is manifested by wide spread narrowing of the airways in allergic asthma, bronchoconstriction and bronchial secretion are the results of an immediate hypersensitivity reaction [1]. Bronchial asthma is one of the most disabling diseases, affecting nearly 7-10% of world population [2]. Worsening of asthma during sleep is referred to as "nocturnal asthma" an asthma phenotype [3]. A study of patients with nocturnal asthma reported that approximately 94% of dyspneic episodes occurred between the hours of 10 PM and 7 AM, with 4 AM the time of peak symptom frequency [4]. It is reported that 70% of sudden deaths and 80% of cases of respiratory arrest in active asthma occur during sleep-related hours [5]. A new therapeutic method called chronotherapy has been recently considered for the treatment of asthma. Chronotherapy of asthma aims to provide a more rational approach to treatment and also reduce side effects. Asthma is well suited for chronotherapy because broncho-constriction and exacerbation of symptoms vary in a circadian fashion [6, 7]. According to the World Health Organization traditional medicine or herbal medicine is the accumulation of the knowledge, skills, and practices based on the theories, beliefs, and indigenized by different cultures, to maintain health [8]. Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products, which contain as an active ingredients parts of plants, or other plant materials, or combinations. Herbal treatments are the most popular form of traditional medicine, and are highly lucrative in the international marketplace [9].

The currently used drugs for the treatment of asthma are so far from satisfactory as they provide only symptomatic relief; produce several adverse effects, like muscle tremor and hypokalemia are major adverse effects of β2 agonists. Hence, ayurveda has recommended a number of drugs from indigenous plant sources for the treatment of asthma and allergic disorder, and have been successful in controlling these diseases as well. Some herbal drugs which are mainly used in treatment of asthma are, Albezzia Lebbeck, Euphorbia Hirta, Adhatoda Vasica and Allium Capa [10]. Vasaka consists of fresh, dried, mature leaves of Adhatoda vasica Nees (Fam.Acanthaceae), a sub-herbaceous bush, found throughout the year in plains and sub-Himalayan tracts in India [11]. Important chemical constituents of leaf include pyrroloquinazoline alkaloids, vasicine, vasicol, adhatonine, vasicinone, vasicinol, vasicinolone. Vasicine was reported to have bronchodilatory, respiratory stimulant and uterine stimulant effect. Vasicinone was shown to have bronchodilatory, weak cardiac stimulant and antianaphylactic action. In Ayurvedic preparations, Vasaka leaf juice (Vasa swarasa) is incorporated in more than 20 formulations. This method is not applicable in large scale extraction of juice for commercial

purpose [12]. In case of solid dosage forms, Adhatoda vasica is presently available as single drug formulation in capsule and powder dosage forms. It is also available in capsule dosage form for polyherbal formulation. Formulation of Adhatoda vasica leaf powder into a tablet dosage form might ensure dosage precision, since herbal medicines have been widely criticized due to lack of standardization. Also formulation of Adhatoda vasica into a modern pharmaceutical conventional tablet dosage form would confer into many of the good properties of tablets [13]. In the present study, it was aimed to develop novel enteric coated tablet formulation of vasaka using superdintegrants in the core and dual polymers as coat. These coats remain intact in stomach, and dissolve in small intestine providing the essential lagtime and allowing the drug to release when it is actually needed, thereby achieving the chronotherapy for nocturnal asthma.

II. MATERIALS AND METHODS

Vasaka pure powder was purchased as "ADULSA'' from Dr.Jain's Forest Herbals Pvt. Ltd. Songir - Maharashtra. Vasicine (>97% pure by HPLC) standard was purchased from Natural Remedies, Bangalore. Eudragit S 100, Ethyl cellulose was obtained as gift samples from Glenmark Pharmaceuticals Ltd., Mumbai. Acetone, Polyethylene glycol, Talc was procured from S. D. Fine chemicals Pvt. Ltd, Mumbai. Diethyl Pthalate was gifted from Pellet Pharma, Hyderabad. All other reagents used were of analytical grade.

2.0 Methods

2.1. Identification and authentication of herbal drug Adhatoda vasica (Vasaka)

The procured sample of herbal drug vasaka was identified and authenticated by the Department of Pharmacognosy, N.E.T. Pharmacy College, Raichur, India. The pure powder sample of vasaka was subjected to various tests for the presence of phytoconstituents like carbohydrates, proteins, amino acids, sterols and triterpenoids, glycosides, alkaloids, phenolic compounds, tannins and steroidal glycosides, characteristic of the drug [14].

2.2. Quantification of Vasaka by UV / UV method for analyzing Vasaka

Vasicine was reconstituted with 1 ml of saline and the absorbance measured at λmax of 281 nm using an UV spectrophotometer. A stock solution of vasicine 10 µg/ml solution in 0.1N HCl and pH 6.8 phosphate buffers was prepared using an ultrasonic bath. From this stock solution a series of dilutions,(1,2,3,4,5,6,7,8,9 and 10 µg/ml) were prepared using respective mediums. Absorbance was measured using UV spectrophotometer at λ max 281 nm and the standard graph plotted with concentration (µg/ml) on the abscissa and absorbance on the ordinate [15].

2.3. Formulation of vasaka core tablet

Core tablets containing 300 mg of vasaka powder were prepared by direct compression method. Superdisintegrant cross caramellose sodium was used in varying concentrations (2.5 – 7.5% w/w). The drug, diluents and superdisintegrant were passed through sieve no.40 and mixed together in a plastic container. Magnesium stearate and aerosil passed through sieve no.80 were mixed and blended with above mixture. The mixed blend of excipients was compressed into tablets using 10 mm flat punches on a 10 stationed rotary compression machine (Rimek, Ahmedabad, India). The core tablet formula is given in TABLE 1.

Table 1: Formulae of vasaka core tablets

Ingredients	**Batch code**		
Quantity per tablet (mg)	**A**	**B**	**C**
Vasaka powder	300	300	300
Cross caramellose sodium	10	20	30
Lactose	50	40	30
Starch	30	30	30
Magnesium stearate	8	8	8
Aerosil	2	2	2
Total weight (mg)	400	400	400

2.3.1. Optimization of vasaka core tablets

The core tablets were optimized based on the disintegration time. Once a tablet disintegrates, the characteristics of the drug, either alone or assisted by other formulation ingredients, determines the dissolution rate and extent of the drug available in solution. The selection of a superdisintegrant and the use level plays a key role in determining the drug release of finished formulations [16]. The optimised formulation from the above batch of tablets was selected for further development as enteric coated formulations for treatment of nocturnal asthma.

2.3.2. Enteric coating process for optimized vasaka core tablets

The optimised core tablet formulation of vasaka was first coated with ethyl cellulose (EC), a pH independent polymer as Inner hydrophobic layer and later it was coated with pH dependent polymer Eudragit S 100 (ES 100) as outer layer. The inner and outer polymer coats were applied by using conventional pan coating system (CIP Machinaries Private Limited, Ahmedabad. India). Different levels of coating of Inner and outer polymeric layers are shown in TABLE 2. The composition of coating solutions is given in TABLE 3.The conditions of coating operation are given in TABLE 4. The technical details relating to preparation of ethyl cellulose inner coating solution and Eudragit S 100 outer coating solution are described in an earlier publication [17]. A structure of the supposed enteric coated herbal DDS of vasaka is shown in "Fig. 1".

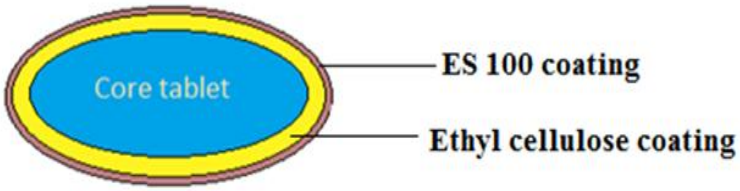


Figure 1: Structure of enteric coated vasaka drug delivery system.

2.3.3. Development of enteric coated vasaka drug delivery system (ECVDDS)

As discussed earlier the vasaka enteric coated tablets are prepared in two stages of coating process. In the first stage the vasaka core tablets were first coated with ethyl cellulose. The EC polymer solution was sprayed on to the prewarmed tablet bed in a conventional pan coating apparatus. The coating process was repeated till the desired levels of coatings were achieved. The coated tablets were dried in the coating pan for 15 mins at the end of the process. The % mass increase of the tablets upon coating was taken to be indicative of the coat thickness. Seven different formulations were obtained by coating the tablets at different levels from 2.5 to 30% w/w (TABLE 2) [18]. In the second stage, enteric coating of EC coated tablets was performed. Different EC coated formulations were coated with pH sensitive polymer Eudragit S100. The coating level was optimized and coating level of 2.5% as total solid applied was found sufficient to protect the tablet from disintegrating in gastric fluid. Tablets were placed in the pan and coating solution was sprayed and dried with the help of inlet air. The coating process was repeated till the desired level of coating was achieved. The tablets were further dried in the coating pan for 10 mins.

The % weight gain of enteric coated vasaka tablets was calculated using the following equation:
% weight gain = (Wt – Wo)/Wo X 100 --- (1)
Where Wt is the weight of the tablet after coating, Wo is the initial weight of tablet [19].

Table 2: Coating levels of inner and outer polymers.

Formulation	Inner layer	Outer Enteric layer
	Ethyl cellulose % w/w	Eudragit S 100 % w/w
CF1	2.5	2.5
CF2	5.0	2.5
CF3	10	2.5
CF4	15	2.5
CF5	20	2.5
CF6	25	2.5
CF7	30	2.5

Table 3: Composition of coating solutions

Inner Layer		Outer Layer	
Ingredient	**Use**	**Ingredient**	**Use**
Ethyl cellulose	hydrophobic polymer	Eudragit S100	pH dependent polymer
Diethylpthalate	plasticizer	PEG 400	plasticizer
Acetone	solvent	Acetone	solvent
Talc	glidant and antitacking agent	Talc	glidant and antitacking agent

Table 4: Process parameters of polymer coating for ECVDDS

Apparatus conditions	Inner layer Ethyl cellulose	Outer layer Eudragit S 100
Inlet temp (°C)	50-55	40-45
Exhaust temp (°C)	40-45	30-35
Spray rate (ml /min)	3-5	5
Spray gun distance from tablet bed (cm)	10 – 15	10 – 15
Pan Speed (rpm)	25	25

2.4. Evaluation of vasaka core tablets

Vasaka core tablets developed were evaluated for the various post-compression parameters like thickness, diameter, hardness, weight variation, friability, drug content and in-vitro disintegration studies. The core tablets were compared with a marketed vasaka tablet (Adusa tablet) for disintegration time, in order to select the best immediate releasing core formulation.

2.5. Evaluation of enteric coated vasaka drug delivery system

2.5.1. Film thickness

The thickness of ten randomly selected tablets from each batch of coated tablets was individually recorded in mm using a vernier calliper. The mean and standard deviation values were calculated from each value recorded.

2.5.2. Weight variation

The weight variation of the coated tablets was determined by official method as given in IP. The percentage difference in the weight variation for each batch of coated tablets was computed from average tablet weight of each batch. Ten tablets were used for weight variation test.

2.5.3. Drug Content

10 tablets were weighed individually and powdered. Equivalent to one tablet of theoretical drug content was weighed and dispersed in 100 ml of pH 6.8 buffer and was subjected for sonication for 15 mins. The content was filtered suitably diluted and measured. Average content of vasicine was determined by using UV-Vis spectrophotometer (UV-2450, Shimadzu, Japan) at λ max 281 nm against blank reagent. Test was performed in triplicate and drug content was calculated by using the following equation [15, 20]:

$$\text{Drug content (mg)} = \frac{(\text{Absorbance} \times \text{Slope} \pm \text{Intercept}) \times \text{Dilution factor}}{1000} \quad \text{----- (2)}$$

2.5.4. Scanning electron microscopy (SEM)

Surface roughness is an important parameter in pharmaceutical tablet dosage forms. SEM has been extensively used to characterize the morphology and surface topography of the coated tablets [21]. The optimized vasaka enteric coated and uncoated core vasaka tablets were subjected for scanning electron microscopy. The samples to be examined were mounted on the SEM sample stub using a double sided sticking tape. The samples mounted were coated with gold (200 A^0) under reduced pressure (0.001 torr) for 5 mins using an ion sputtering device. The gold coated samples were observed under the SEM and photomicrographs of suitable magnifications were obtained.

2.5.5. Disintegration time

The disintegration time for the enteric coated vasaka drug delivery systems was carried out using USPXXIII (Electrolab, Bangalore, India) disintegration tester. Six enteric coated tablets were placed in each tube of the apparatus; the disintegration test was performed initially in pH 1.2 without the discs for two hours. After 2 hrs, the same tablets were tested for disintegration in mixed pH 6.8 phosphate buffer as medium with the discs. The temperature of the water bath was maintained at 37 ± 5°C throughout the test. The disintegration time for the tablets was recorded in minutes. The test was carried out in triplicate and mean was taken [22].

2.5.6. Lag time of vasaka drug delivery systems (Rupture test)

The time at which the outer coating layer starts to rupture is defined as the lag time. The intention of the study was to develop enteric coated vasaka tablets which remain protected from gastric environment and will release the drug rapidly in the intestine after administration. Providing suitable lag time for the enteric coated tablets would serve the purpose. Hence Lag time was determined, by placing the coated tablets in USP dissolution apparatus II containing 900 ml of 0.1 N HCl for initial 2 hrs and then changing to phosphate buffer of pH 6.8 till the coating ruptures. The media was agitated at 50 rpm and maintained at 37±0.5°C. The time

taken for outer coating to rupture was visually monitored and reported as lag time. In addition to the rupture behavior; the enteric coated vasaka tablets were photographed by a digital camera [23, 24].

2.5.7. Effect of inner layer concentration on lag time

The optimized core tablets of Batch C were coated with different levels of ethyl cellulose as inner layer to obtain the required lag time. The core tablets of Batch C were coated with 2.5, 5, 10, 15, 20 and 25%w/w of ethyl cellulose and obtained formulations were subjected to in vitro dissolution study. Effect of ethyl cellulose layer concentration over lag time and release behavior was observed using a spectrophotometer, as described in the method under in vitro drug release studies.

2.5.8. In-vitro dissolution studies

Dissolution studies of the enteric coated vasaka tablets were carried out in triplicate, employing USP type-II apparatus (USP XXIII Dissolution Test Apparatus) following conditions that simulate gastrointestinal tract. 0.1N HCl and phosphate buffer of pH 6.8 were used as dissolution medium. The temperature of the dissolution medium was maintained at 37 ± 0.5^0C with a stirring speed of 50 rpm. Initially tablets were subjected to dissolution in 0.1N HCl for 2 hrs and after that media were changed to phosphate buffer pH 6.8. The samples were withdrawn at regular intervals of time and analysed for presence of drug by UV spectrophotometer at 281 nm. The concentration of the drug was determined from standard calibration curve. The dissolution data was analysed for knowing the amount of drug released and percentage cumulative drug released at different time intervals [22].

2.5.9. Drug release kinetics

In order to study the mechanism of drug release from the prepared vasaka enteric coated drug delivery systems, the release data obtained was evaluated using zero-order release kinetics (Eq. 3), first order kinetics (Eq. 4), Higuchi's square root of time equation (Eq. 5) [25] and Korsemeyer and Peppas equation (Eq. 6) [26, 27].

$$M_t = M_0 + k_0 t \qquad (3)$$

where M_t is the amount of drug dissolved in time t, M_0 is the initial amount of drug in the solution, k_0 is the zero-order release rate constant and t is the release time,

$$M_t = M_0 e^{-kt} \qquad (4)$$

where M_t is the amount of drug dissolved in time t, M_0 is the initial amount of drug in the solution, k is the first-order release rate constant and t is the release time,

$$M_t = k_h \sqrt{t} \qquad (5)$$

Where M_t is the amount of drug dissolved in time t, k_h is the Higuchi dissolution constant and t is the release time,

$$M_t/M_\infty = k_s t^n \qquad (6)$$

where, M_t and M_∞ are the cumulative amount of drug released at time t and infinite time, respectively; k_s is a constant incorporating structural and geometric characteristics of the device, and n is the drug release exponent, indicative of the mechanism of drug release. The values of n assigned to a cylinder are 0.45 for Fickian diffusion (case I) and $0.45 < n < 0.89$ for non-Fickian (anomalous) diffusion; and > 0.89 indicates super case II type of release respectively. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.

2.6. Stability studies

The stability studies were carried out for the optimized formulation at 40°C/75% RH for a period of three months. The sample tablets were wrapped in the laminated aluminum foils and were placed in the accelerated stability chamber at 40°C/75% RH for a period of three months. Sampling was done at a predetermined time intervals. The tablets were evaluated for their general appearance; drug content, lag time and in vitro drug release study [28].

III. Results and Discussion

The current pharmacotherapeutic approaches to asthma have several limitations. First, there is no known asthma cure and little evidence that prevention is possible in susceptible persons. Hence, patients continue to be at risk of symptoms and exacerbations and the medications have adverse effects. Mortality remains a severe problem. At the same time, a large number of medicinal plants are used in the treatment of asthma. Many drugs commonly used today are of herbal origin. In the present study a novel formulation of herbal drug vasaka in the form of time release tablet was tried and which is economical in terms of time and machinary usage. The enteric coated vasaka drug delivery system developed in the present study was a reservoir device where the tablet core was surrounded by two consecutive layers, a hydrophobic inner layer and an outer

rupturable layer. Ethyl cellulose was coated as inner layer to avoid premature drug release in lower pH-media and to increase the lag time because of its reduced wettability, media uptake and erosion properties. Eudragit S 100 which hydrates and swells due to the presence of quaternary ammonium groups was selected as enteric coating polymer. Eudragit S 100 coating was given to the ethyl cellulose coated core tablets to achieve ideal drug delivery system for treatment of nocturnal asthma.

3.0. Identification and authentication of herbal drug Adhatoda vasica (Vasaka)

As much literature is not available related to herbal drugs, in the present study the authenticity of the drug used and its pharmaceutical properties had to be studied, hence the vasaka pure powder was subjected to minimum pharmacognostical and pharmaceutical analysis. The results of prelimnary qualitative analysis revealed the presence of following functional groups (TABLE 5). The obtained results were in accordance with those mentioned in reference books [29, 30]. As the reported results met with the minimum standards the powder was considered pure and was utilized was further research work.

Table 5: Pharmacognostical evaluation of Vasaka pure powder

Sl.No	Functional group	Vasaka powder results
1	Carbohydrates	+ ve
2	Proteins amino acids	+ ve
3	Sterols and triterpenoids	+ ve
4	Glycosides	+ ve
5	Alkaloids	+ ve
6	Phenolic compounds	+ ve
7	Tannins	+ ve
8	Steroidal glycosides	+ ve

3.1. Quantification of Vasaka by UV / UV method for analyzing Vasaka

The major alkaloids present in vasaka are vasicine and vasicinone which are present in all parts of the plant. The leaf extract has been used for the treatment of bronchitis and asthma for many centuries. Vasicine is reported to have bronchodilatory, respiratory stimulant and uterine stimulant effect [12]. Vasicine, at low concentrations, induced relaxation of the tracheal muscle. At high concentrations, vasicine offered significant protection against histamine induced bronchospasm in guinea pigs [31]. Hence in the present study Vasicine was estimated by UV to quantify the amount of vasicine present in the prepared herbal drug delivery systems. "Fig. 2" indicates the λmax determination of vasicine using UV spectrophotometer. The standard plot was found to be linear for the concentrations studied with a linear regression coefficient R2 of 0.998. The Vasicine content in the developed formulations were determined by using the standard curve for vasicine. The regression coefficient of calibration curve was 0.998 and the curve was linear from 1–10µg.

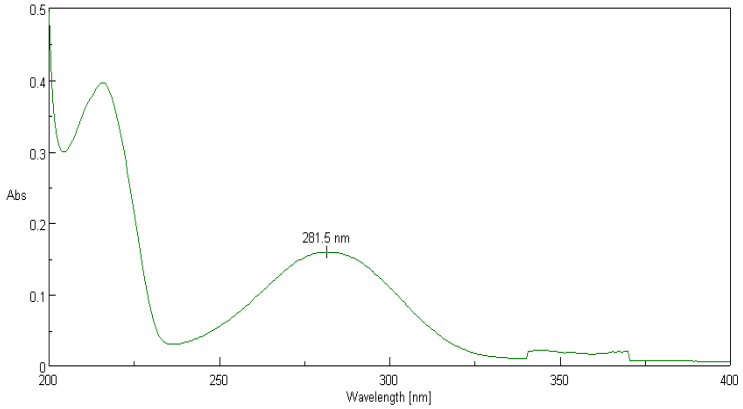


Figure 2: λmax determination of vasicine using UV spectrophotometer.

3.2. Evaluation of vasaka core tablets

The different batches of vasaka core tablets were subjected to various evaluation tests for thickness, diameter, hardness, weight variation, friability and drug content studies. TABLE 6 shows the evaluation results of Post compression parameters of vasaka core tablets. The thickness of all the batch of tablets was in the range of 4.4 – 4.6 mm. The diameter was ranging from 10 -10.1 mm. The hardness was in the range of 2.8 – 3.7 Kg/ cm^2 and was within acceptable limits. The tablets were hard and hardness was found satisfactory for coating purpose, as the tablets will be subjected to rolling and tumbling motion in coating pan. The hardness of herbal tablets is usually found less compared to synthetic drugs because of less binding and attractive forces between

particles. The weight variation was less than 3% and was within acceptable limits. Friability value of less than 1% also supported the fact that tablets had sufficient strength. The drug content uniformity of all the batches was found in the range of 205±1.05 - 231±1.06 mg. The drug content was uniform and within limits indicating the method followed to prepare the powder blend and tablets distributed the vasaka herbal powder uniformly throught the blend. All the batch of tablet showed acceptable pharmacotechnical properties and complied with the in house specifications.

Table 6: Post compression parameters of vasaka core tablets.

Batch Code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Weight variation (%)	Friability (%)	Vasicine content (µg)
A	4.4±0.05	10.00±0.00	2.8±0.11	399.0±2.64	0.75±0.05	205±1.05
B	4.5±0.11	10.07±0.05	3.0±0.20	398.6±2.08	0.67±0.06	220±2.08
C	4.6±0.10	10.10±0.10	3.7±0.41	399.6±0.57	0.76±0.05	231±1.06

3.2.1. Optimization of vasaka core tablets

Three batches of vasaka core tablets A, B, C were prepared. The most important parameter that needs to be optimized in the development of core immediate release tablets is disintegration time of tablets. The disintegration time of the tablets prepared by using different concentration of Cross caramellose sodium was well within the limits. The disintegration time of different batch of tablets was found in the range of 5.3 to 13.6 mins. The superdisintegrant at 7.5% w/w concentration provided the minimum disintegration time of 5.3 ± 0.5 mins compared to 25.3±2.0 mins as given by marketed formulation – Adusa Tablet. "Fig. 3" shows the in-vitro disintegration studies of vasaka core tablets. Thereby the formulation from Batch C containing 30 mg of cross carmellose sodium (7.5% of tablet weight) was considered as optimized formulation. Hence for further research work, formulation from Batch C was utilised.

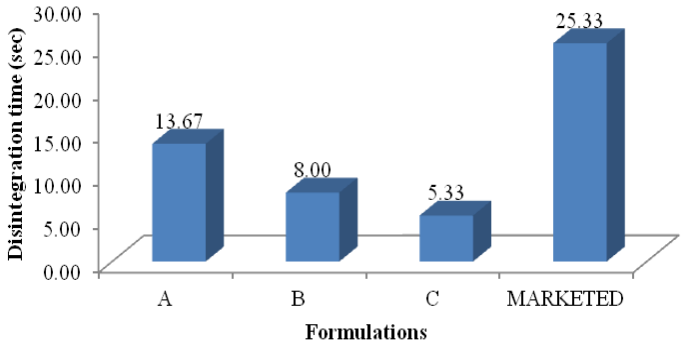


Figure 3: In-vitro disintegration studies of vasaka core tablets

3.2.2. Coating of vasaka core tablets

Most of the time release systems contain a drug reservoir, surrounded by a barrier, which erodes/dissolves or ruptures. These barrier technologies used around the active agent are designed to degrade or dissolve after a certain time, and in those that the degradation of the polymer itself induces the release of the active agent. Ethyl cellulose, a pH independent polymer in different percentages from 2.5 to 30% w/w was applied as barrier coating between the core tablet and enteric coating using pan coating apparatus. This barrier avoids leaching of moisture into tablet core and erodes or dissolves after predetermined lag time. Ethyl cellulose being hydrophobic does not interfere with tablet disintegration and provide the effective barrier from water to achieve the desired lag time required for the time release system. All the ethyl cellulose coated core tablets were pan coated with Eudragit S100 (2.5% w/w) to prevent the drug release in stomach. Eudragit S100 coating dissolves at pH ≥7 and complete release of drug occurs after a suitable lag time in the intestine. The prepared herbal vasaka coated tablets had no visible defects such as orange peel effect, chipping, tacking or any other physical flaws. The coating system followed was dispersed in the minimum amount of time, and produced acceptable weight gains.

3.3. Evaluation of enteric coated vasaka drug delivery system

3.3.1. Film thickness

The thickness of the enteric coated vasaka tablets was found in the range of 4.95 - 6.07 mm indicating fairly acceptable tablets. The mean thickness of the enteric coated vasaka tablets CF1 to CF7 was found to be

4.95, 5.00, 5.32, 5.60, 5.80, 6.01and 6.07 mm respectively (TABLE 7). The thickness of the coated tablets increased with increase in the coat weight applied. The percentage increase in the thickness of tablets was found to be 07.14% - 31.95% for formulations CF1- CF7 respectively.

3.3.2. Weight variation

The Weight variation results of enteric coated tablets are potrayed in TABLE 7. The average tablet weight for the coated tablets was in the range of 421.5 to 533.4 mg. The tablet weight variation was found below 5% for all the batches of coated tablets indicating it was within IP official limit. The percent practical weight gain calculated from the average tablet weight was found to be between 5.37 to 33.48% for all the tablets respectively.

3.3.3. Drug Content

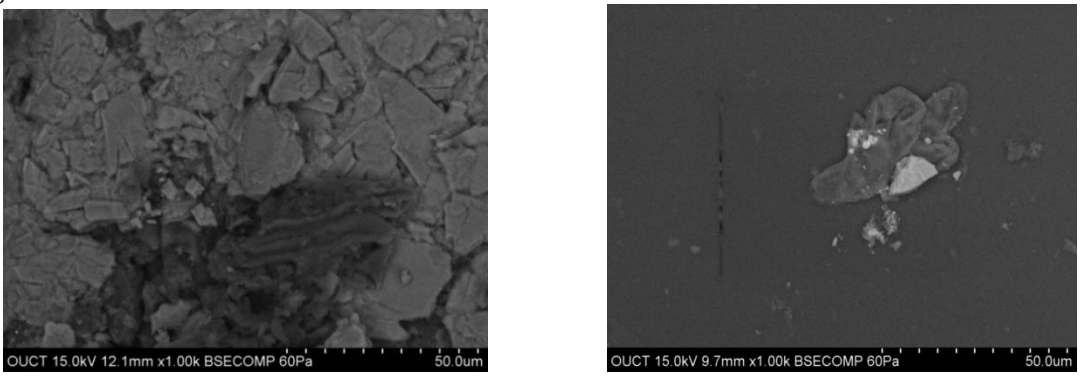
The drug content of all the formulations was found to be with-in the official limits. The vasicine content was found in the range of 220±5.29 – 248±6.43µg respectively (within the acceptable range) for all the formulations (TABLE 7). The results proved that coating process did not affect the integrity of tablet and no drug loss occurred during the coating process.

Table 7: Characteristics of enteric coated vasaka drug delivery systems.

Formulation	Thickness (mm) (Mean±SD, n=10)	Weight variation (mg) (Mean±SD, n=10)	Drug Content (µg) (Mean±SD, n=3)
CF1	4.95±0.05	421.5±1.84	240±6.08
CF2	5.00±0.06	431.4±1.95	236±5.03
CF3	5.32±0.07	451.5±2.36	228±4.16
CF4	5.60±0.18	470.6±2.11	220±5.29
CF5	5.80±0.09	490.8±1.68	248±6.43
CF6	6.01±0.13	510.5±2.06	226±4.16
CF7	6.07±0.14	533.4±1.89	225±5.13

3.3.4. Scanning electron microscopy

Scanning electron microscopy provides visual information about the surface morphology of uncoated core tablet from batch C and optimised coated tablet CF6. The SEM results are shown in "Fig. 4 (a) and (b)" respectively. SEM observations of the core and coated tablet could be distinguished clearly. The surface of the core tablet was rough, irregular and lumpy with uneven distribution of particles. In contrast the coated surface of CF6 was fairly smooth, clear and spread evenly. The tight surface free from cracks or pores revealed a distinct continuous and dense coat. The smooth surface indicated the polymers adhered to the tablet surface with a strong interfacial bond.



a) Surface morphology of uncoated core tablet (batch C) b) Surface morphology of optimal enteric coated vasaka drug delivery sytem (CF6)

Figure 4: SEM Photomicrographs

3.3.5. Disintegration time

The results of disintegration studies are given in TABLE 8. The disintegration time for all the tablets was in the range of 25 mins to as long as 260 mins. The formulation CF1 with 2.5% EC coating disintegrated in the 0.1N HCl itself within 25 mins indicating the polymer content did not withstand the medium. Hence tablets with higher polymer content were developed. The formulations CF2 – CF6 coated with 5 - 25%w/w ethyl cellulose and 2.5%w/w Eudragit S 100 polymer remained stable in acid media and disintegrated in alkaline medium. The observed results are in agreement with the reported literature showing the potential of this polymer combination to prevent disintegration in acidic media. The formulations CF2 – CF6 disintegrated in 10 – 140 mins when the

test was done in mixed phosphate buffer pH 6.8. The results indicate that disintegration time in pH 6.8 was found to increase with increase in percent weight gain by tablets. The data also suggested that the disintegration time was independent of the enteric coating weight gain but most likely depends on the inner polymer, in the current experimental condition.

Table 8: Disintegration time of vasaka drug delivery systems.

Formulation	Disintegration Time in simulated gastric fluid (0.1 N HCl)	Disintegration Time in simulated intestinal fluid (pH 6.8)
CF1	Disintegrated in 85 min	-
CF2	No Disintegration up to 120 min	10 min
CF3	No Disintegration up to 120 min	25 min
CF4	No Disintegration up to 120 min	110 min
CF5	No Disintegration up to 120 min	120 min
CF6	No Disintegration up to 120 min	140 min
CF7	No Disintegration up to 120 min	240 min

3.3.6. Lag time of vasaka drug delivery systems (Rupture test)

In the present study all the formulations were coated with different levels of ethyl cellulose (2.5 to 25% w/w) as inner layer and pH sensitive polymer Eudragit S 100 (2.5% w/w) as outer layer. It was observed that lag time was strongly influenced by composition and level of coating. In case of formulation CF1 the lag time was low and was not sufficient to contain the core tablet and the tablet eventually ruptured within 2 hrs. However with formulations CF2 – CF6 enhanced lag time essential for time release was noticed which solely explains the significant role of inner ethyl cellulose layer in providing the lag time. The formulations CF4 – CF7 provided more than two hours of lag time i.e., 225 mins to 380 mins. This can be attributed to the hydrophobic nature of ethyl cellulose and the high amount of coating. The results are displayed in "Fig. 5". The aim of the study was to develop a tablet which will be protected from gastric environment and will release the drug rapidly in the intestine after 3-5 hours of administration. The formulations CF4 – CF7 possibly meet the above expectations. "Fig. 6" depicts the rupture behavior of the enteric coated vasaka drug delivery system at different time intervals. Once the outer polymeric coat is dissolved, it results in weakening of the strength of the coat and rapid burst of coat takes place releasing the drug instantly in to the medium.

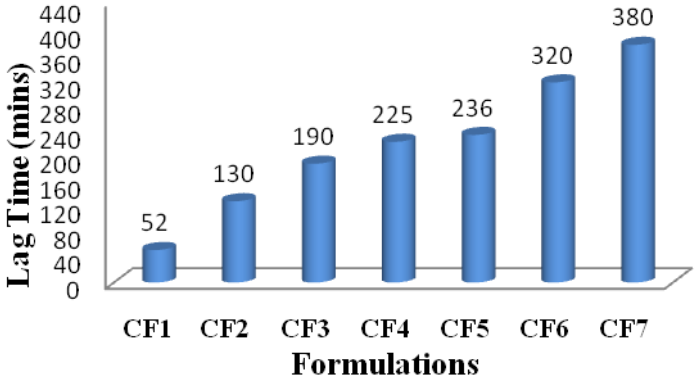


Figure 5: Rupture test (Lag Time) of enteric coated vasaka drug delivery system.

A (0 hrs) **B (4.25 hrs)** **C (6.0 hrs)**

Figure 6: Rupture sequence of enteric coated vasaka drug delivery systems.

3.3.7. Effect of inner layer concentration on lag time

Ethyl cellulose was coated as inner layer at different levels to achieve the required lag time. It was noticed that as the concentration of ethyl cellulose was increased from 2.5 – 30%w/w the lag time also increased from 52 mins to 380 mins. Increase in coat thickness also caused resistance to water penetration and coat rupture. As revealed in Fig. 5, with the increase of coat thickness, there was a corresponding increase in the lag time and subsequent delay in drug release. Thus, percent coating mass gain was found to be another crucial parameter in the modulation of lag time and in achieving the desired drug release profile. A plot of percentage ethyl cellulose mass gain against lag time showed a good linear relationship, as shown in "Fig. 7" (R^2 = 0.955) indicating the vitality of this factor in lag time modulation.

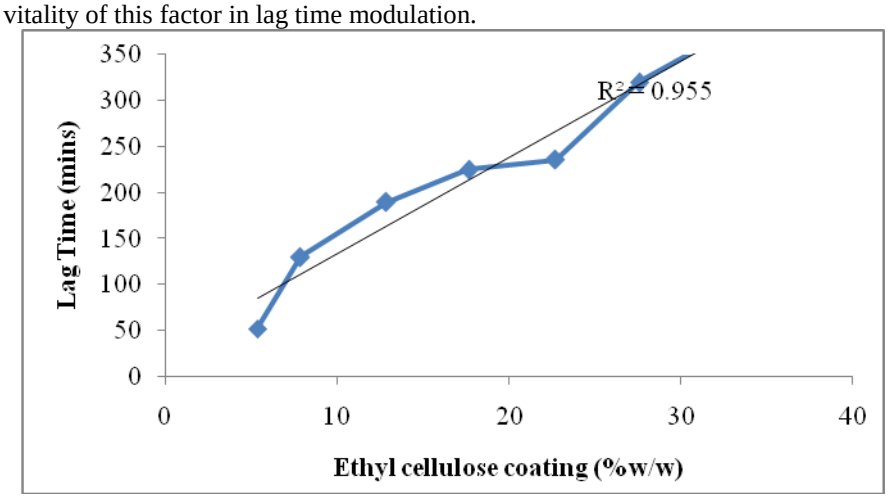


Figure 7: Plot of percent ethyl cellulose mass gain vs. lag time.

3.3.8. In-vitro dissolution studies

In- vitro drug release studies was carried out for all the seven vasaka enteric coated time release formulations in simulated gastric environment (pH 1.2) for 2 hrs and then in simulated intestinal environment of pH 6.8. All formulations released the drug in the range of 74.83 to 98.0% in about 6.00 to 12.25 hrs. Formulations CF1, CF2, CF3 CF4 and CF5 released 98.0, 89.87, 88.10, 83.14 and 74.83% of drug at the end of 6.25 hrs "Fig. 8". In case of ECVDDS CF1- CF5 it is evident from the nature of the graph that the outer Eudragit S 100 coating at 2.5%w/w and inner ethyl cellulose coating between 2.5 – 20%w/w were unable to hold the core tablet from rupturing. This indicated that the lower level of coat polymer weight was insufficient to prevent the premature drug release. In fact the low coat thickness film formed around the core tablet retards drug release but diffusion of drug continues through such a film. The rapid release of drug in initial hours of dissolution study from these tablets suggested need for greater degree of mechanical strength of the coating. From these observations, it could be assumed that the first step in drug release was penetration of water in the core tablet by diffusion through Eudragit film and the rate and amount of water entered was dependent on film thickness. The penetration rate of water accelerated in to the core tablet due to outer polymer chain relaxation. When water reached the core tablet, the superdisintegrant creates internal pressure causing the core to burst and promotes rapid drug release after the coat ruptures. The weakly held fragments of porous core tablet disaggregated into relatively fine particles under the rotating movement of the paddle. As a result the total water contact area with drug was enhanced and thereby maximum dissolution of drug was noticed. A cronomodulated release profile should be characterized by a lag time followed by rapid and complete drug release. After the desired lag time, the onset of release can be achieved by action of superdisintegrant in the core tablet. To achieve the above objective the formulations CF5 – CF7 were designed by increasing the coating level of inner layer up to 30%w/w. Formulations CF5, CF6 and CF7 released 74.83, 91.46 and 95.95% of drug in 6.25 – 12.25 hrs. The percent drug released versus time plot of these formulations revealed that they provided the needed lag time for chronomodulated delivery and also resisted the acidic medium up to 2 hrs. These plots also showed that the dissolution rate was inversely proportional to the thickness of the coat applied. As represented in Figure 5 the lag time for CF5 – CF7 was 236, 320 and 380 mins respectively. The lag time increased with increase in inner ethyl cellulose coating level due to greater degree of mechanical strength of the thick coating which lowers rupturing. This made the outer acrylic coat more impermeable and drug release was retarded. The water uptake capacity and drug release before the rupture of tablet was dependent on outer acrylate polymer coating and inner ethyl cellulose layer. Slowly as the outer coating solubilized, drug dissolution through it was facilitated. These findings were equally supported by disintegration studies of the enteric coated time release tablets. The optimum coating level to obtain a suitable lag time and to initiate drug release at the target site (lower small intestine or

lleocolon junction), was found with 2.5% (w/w) of Eudragit S 100 and 25% (w/w) of ethyl cellulose polymeric film i.e., formulation CF6.

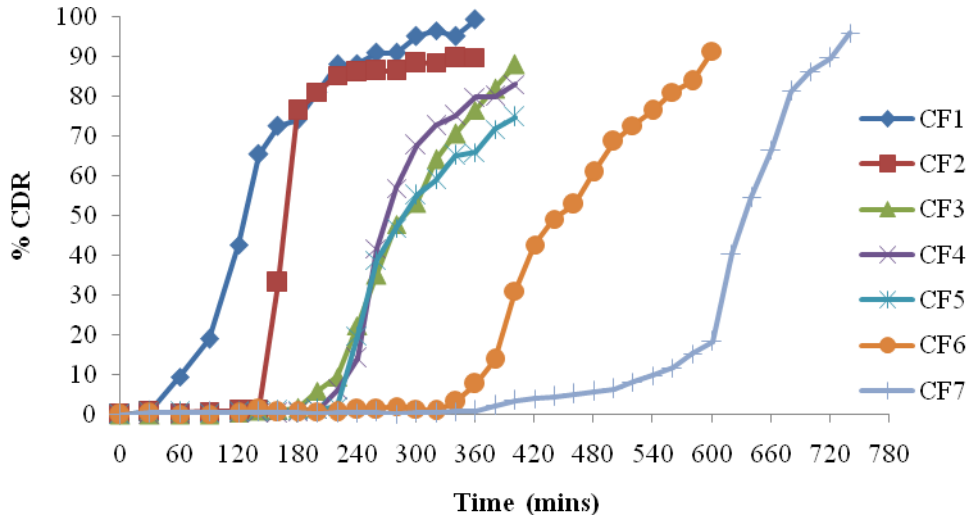


Figure 8: Cumulative percent of drug released versus time profile of enteric coated vasaka drug delivery systems

3.3.9. Drug release kinetics

Values of the coefficient of determination for all the release models obtained for ECVDDS CF1 – CF7 are given in TABLE 9. A comparative study of these values clearly showed that the first order model was the best-fit model for the batches prepared during the study except CF1and CF2. The values of regression in the Korsemeyer and Peppas model (i.e., R^2) were close to unit in all cases excluding CF6 and CF7. The n values were in the range of 0.58 – 0.90 indicating non-Fickian (anomalous) diffusion type of release. The drug release is attributed to the erosion of the outer Eudragit S100 film, which leads to the formation of pores that facilitate drug dissolution due to diffusion.

Table 9: Comparative release model characteristics of ECVDDS

Formulation	Zero order	First Order	Higuchi's	Korsemeyer and Peppas
CF1	0.876	0.602	0.893	0.872
CF2	0.802	0.757	0.720	0.773
CF3	0.835	0.922	0.628	0.903
CF4	0.797	0.869	0.601	0.745
CF5	0.809	0.856	0.610	0.674
CF6	0.773	0.909	0.582	0.722
CF7	0.564	0.865	0.404	0.585

3.4. Stability studies

The stability studies of optimum formulation CF6 done at 40°C/75% RH over a period of three months revealed no change in physical appearance, no significant reduction in the drug content, lag time and drug release (TABLE 10).

Table 10: Stability studies of enteric coated vasaka drug delivery systems at 40°C/75% RH

Formulation	Drug content (mg) (Mean±SD, n=3)	Lag Time (mins)	%Cumulative drug released
CF1	236±1.02	48	96.00
CF2	230±1.12	122	86.24
CF3	232±2.06	186	84.36
CF4	226±3.24	230	80.56
CF5	250±4.22	232	75.62
CF6	230±2.00	310	90.12
CF7	220±4.02	369	96.44

IV. CONCLUSION

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Novel drug delivery technology when applied for herbal medicine may help in increasing the efficacy and reducing the side effects of herbal compounds. This was the basic idea behind developing enteric coated vasaka drug delivery systems. Thus in the present study vasaka enteric coated tablets were developed and evaluated that deliver the drug at specific time as per the pathophysiological need of the disease resulting in improved patient therapeutic efficacy and compliance. ECVDDS show rapid release of drug after a lag time. The principle rationale for the use of timed release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. To achieve this, vasaka core tablets were coated with composition of inner ethyl cellulose and outer enteric Eudragit S-100 polymer. This coating composition i.e., 2.5w/w of Eudragit S-100 and 20 – 30%w/w of ethyl cellulose helped achieve a definite non-release lag phase. The enteric coated vasaka drug delivery system prevented drug release in stomach and released drug rapidly after predetermined lag time in the intestinal tract when pH was above 6. The intention was to administer the formulation at around 10.00 pm so that after a specified lag time the drug is rapidly available in the early morning hours to treat nocturnal asthma. The formulation CF6 with 25%w/w coating of inner ethyl cellulose layer was considered optimized one as it provided 320 mins of lagtime and 91.46% of drug release at the end of 10 hrs. Hence the vasaka herbal drug delivery systems are worth evaluating for further in-vivo studies for chronotherapeutic treatment of nocturnal asthma.

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