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Fabrication and Evaluation of Mini Tablet Filled Capsules to Treat Transient Ischemic Attack

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In this work, mini tablets filled hard gelatin capsules were fabricated for a fixed-dose therapy for transient ischemic attack (TIA). Clopidogrel besylate (CB)-75 mg and acetyl salicylic acid (ASA)-75 mg were utilized in this work. Among the mini-tablets (MTs) clopidogrel besylate, was uncoated conventional mini-tablets, whereas acetyl salicylic acid was enteric-coated. Acetyl salicylic acid gastric irritation was overcome by using *Plantago ovata* seed mucilage as a binder in all mini-tablets. Both types of mini-tablets were filled in hard gelatin capsules. Clopidogrel besylate and acetyl salicylic acid compatibility with excipients used were evaluated, all the mini-tablets were judged for post-compression constraints. The prepared mini-tablets confirmed no interaction by FTIR and DSC studies. All the mini-tablets passed the physico-chemical constraints. Clopidogrel besylate was released from the dosage form within 45 min, whereas enteric-coated acetyl salicylic acid mini-tablets resist to release in an acidic environment and released within 45 min in an alkaline buffer. Even the filled capsules were also passed all the parameters evaluated. The study concludes that by using *P. ovata* as a binder in making tablets will resolve the issues related to gastric irritation.

Keywords: Mini tablets, Capsules, Release, Gastric irritation, Mucilage, Ischemic attack.

INTRODUCTION

A transient ischemic attack (TIA) is an impermanent duration of signs like a stroke [1]. A transient ischemic attack persists for a few minutes without any perpetual impairment [2]. Transient ischemic attack is also known as a mini-stroke [3] and 1 among the 3 patients with a stroke, later it converts into a transient ischemic attack in 6 months [4]. A transient ischemic attack is a signal for the stroke and which can be prevented.

Mini tablets are small tablets with uniform shapes, sizes and weights. Different types of tablets can be easily filled in capsules for achieving the desired effects [5]. They are preferred because of their uniformity in drug, sizes, ease of preparation and low cost compared to pellets and granules [6]. The most commonly used drugs for post-operative heart attacks are antiplatelet drugs like acetyl salicylic acid and clopidogrel [7]. The grouping of clopidogrel besylate and acetyl salicylic acid, required for less-educated patents. The long term therapy of acetyl salicylic acid causes stomach ulcers, which cannot be resolved by the co-administration of proton pump inhibitors (PPIs) and their use is restricted as they interact [8] with acetyl salicylic acid and clopidogrel besylate.

Some attempts have been made with the grouping of clopidogrel besylate and acetyl salicylic acid but pointed out the issues related to gastric irritation [9]. In such cases proton pump inhibitors use in combination therapy but, they concluded with compatibility issues. So, a need came to resolve all these issues, by a co-administration of some gastroprotective excipients. By doing extensive literature the authors found *Plantago ovata* mucilage which proved to have gastric protective activity [10-13] and successfully used in the management of stomach and duodenal ulcers. By this approach, the adverse effects of acetyl salicylic acid can be overcome with ease. Moreover, the past work also proved *P. ovata* mucilage as a tablet binder [14-16].

In this study, the authors used *P. ovata* seed mucilage as a binder in making tablet granulation and compressed them to

mini-tablets (uncoated clopidogrel besylate and enteric coated acetyl salicylic acid) and filled into human chorionic gonadotropin (hCG).

EXPERIMENTAL

Clopidogrel besylate was gifted from U.S.V. Pvt. Ltd, Mumbai, India whereas acetylsalicylic acid from Waksman Selman pharmaceutical Pvt. Ltd. Anantapur, India. Lactose, microcrystalline cellulose (MCC), magnesium stearate, talc, ethyl cellulose and hydroxypropyl methylcellulose (HPMC) phthalate were purchased from Qualigens Fine Chemicals, Mumbai, India. Empty hard gelatin capsules (size '1') were gifted from Hetero Drugs, Hyderabad, India. The remaining ingredients used were of AR grade.

Fourier transform infrared (FTIR) analysis: Pure drugs (clopidogrel besylate and acetyl salicylic acid) compatibility with excipients of this study were studied with 2 mg of sample compressed to pellet with 200 mg of KBr and scanned between 4000-400 cm^{-1} with a resolution of 1 cm^{-1} (Perkin-Elmer, Spectrum-100, Japan).

DSC studies: DSC thermograms of pure drugs (clopidogrel besylate and acetyl salicylic acid) and their blends were documented using diffraction scanning calorimeter (DSC 60, Shimadzu, Japan) by heating from 30 to 350 ºC at the rate of 10 ºC/min.

Isolation of *P. ovata* seeds mucilage: *P. ovata* seeds were sodden in ~20 times of distilled water for 48 h. Then the seeds were boiled for 10 min by that the mucilage gets completely discharged into water. Later the mixture was squeezed using a muslin cloth to eliminate marc and filtrate was collected. To this same quantity of acetone was added to precipitate the mucilage. Then the mucilage was detached and dried in an oven (< 60 ºC), powdered, sieved (# 80 mesh), weighed and stored in a desiccator [17-20].

Preparation of clopidogrel besylate mini-tablets: The ingredients (Table-1) screened (#40 mesh) and mixed for 3 min. To this blend, magnesium stearate and talc (screened #60) were added and mixed in the polybag for 3 min. The blend was compressed to get mini-tablets [21].

Preparation of acetyl salicylic acid enteric-coated mini-tablets: The enteric-coated tablets for delayed-release has these steps [22-25].

Preparation of core tablet: The ingredients (Table-2) screened (#40 mesh) and adopted the same method as metioned in the clopidogrel besylate mini-tablets for the preparation of core tablets.

Sub-coating of acetyl salicylic acid: The core tablets so formed were made water-proof by sub-coating using ethyl cellulose (2.0 mg) and its optimized parameters for sub coating are given in Table-3.

Enteric coat composition: The waterproofed sub coated tablets were subjected to gastric resistant enteric coating (Table-4) and its optimized parameters are given in Table-5.

Development of fabricated mini-tablets capsules (MTFC): Three mini-tablets each of clopidogrel besylate and acetyl salicylic acid were filled manually into empty capsule and closed with a cap and coded (Table-6). The connection between the capsule body and cap was sealed by applying water with a micro brush [26].

Evaluation of mini-tablets

Pre-compression parameters: Bulk and tapped densities, Carr's index, Hausner's ratio and angle of repose were appraised for the blend of mini-tablets.

Post-compression parameters: Parameters like thickness, hardness, weight variation, friability, *etc.* were appraised for the prepared mini-tablets [27-30].

Weight variation of mini-tablets: The weight of 20 mini-tablets were individually weighed (MODELS, CAS-54) and the mean was calculated and the deviation was calculated.

TABLE-1
COMPOSITION OF VARIOUS CLOPIDOGREL BESYLATE MINI TABLETS

Ingredient	Formulation								
	CBM-1	CBM-2	CBM-3	CBM-4	CBM-5	CBM-6	CBM-7	CBM-8	CBM-9
Clopidogrel besylate	75	75	75	75	75	75	75	75	75
MCC	107	102	97	92	87	82	77	72	67
Lactose	10	10	10	10	10	10	10	10	10
P. ovate seed mucilage	5	10	15	20	25	30	35	40	45
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
Weight of the tablet	200	200	200	200	200	200	200	200	200

TABLE-2
COMPOSITION OF VARIOUS ACETYL SALICYLIC ACID MINI TABLETS

Ingredient	Formulation								
	ASM-1	ASM-2	ASM-3	ASM-4	ASM-5	ASM-6	ASM-7	ASM-8	ASM-9
Aspirin	75	75	75	75	75	75	75	75	75
MCC	107	102	97	92	87	82	77	72	67
Lactose	10	10	10	10	10	10	10	10	10
P. ovata mucilage	5	10	15	20	25	30	35	40	45
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
Weight of the tablet	200	200	200	200	200	200	200	200	200

TABLE-3
OPTIMIZED PARAMETERS FOR SUB COATING FOR ASPIRIN DR TABLETS

Condition	Pre-heating	Coating	Drying
Inlet air temperature (°C)	55-60	60-65	50
Product temperature (°C)	55-60	50-55	55-60
Outlet air temperature (°C)	35-60	55-60	50-55
Spray rate (mL/min)	–	1-1.5	–
Atomizing air pressure (psi)	–	20	–
Pan speed (rpm)	55 ± 2	55 ± 2	55 ± 2

TABLE-4
ENTERIC COATING FOR ASPIRIN DR TABLETS

Ingredient/tablet	Quantity
HPMC phthalate-55	1.422
Triethyl citrate	0.142
Talc	0.355
Dichloromethane	q.s
Methanol	q.s

TABLE-5
OPTIMIZED PARAMETERS FOR ENTERIC COATING FOR ASPIRIN DR TABLETS

Condition	Pre-heating	Coating	Drying
Inlet air temperature (°C)	55-60	60-65	50
Product temperature (°C)	55-60	50-55	55-60
Outlet air temperature (°C)	35-60	55-60	50-55
Spray rate (mL/min)	–	2-3	–
Atomizing air pressure (psi)	–	30	–
Pan speed (rpm)	55 ± 2	55 ± 2	55 ± 2

Diameter and thickness for mini-tablets: Ten randomly selected mini-tablets from each batch were logged with a Vernier caliper and mean was documented.

Mini-tablet crushing strength/hardness test: Crushing strength of the 6 mini-tablets individually measured using the Pfizer tablet hardness tester (mLabs-SE-276(B). Each mini-tablet is individually placed between the jaws and pressed till it crushes and the mean was recorded.

Friability test for mini-tablets: Ten mini-tablets of clopidogrel besylate were placed in a Friability tester (Veego. VFT-2D) and rotated for 4 min at 25 rpm. The loss on friability can be obtained from the initial and final weights of mini-tablets. On the other hand, this test is not required for mini-tablets of acetyl salicylic acid (as they are enteric-coated).

Disintegration test: The uncoated 6 mini-tablets of clopidogrel besylate were placed in disintegration apparatus (0.1 M HCl) at 37 ± 2.0^{0}C and the time for the breakdown was noted down. Moreover, the enteric coated mini-tablets of acetyl salicylic acid the same procedure was followed, after 2 h, the medium was replaced by 6.8 pH, PBS for 30 min.

Uniformity of drug content: A total of 10 tablets were weighed and powdered. The quantity of powder ≡ 75 mg of clopidogrel besylate was dissolved in 100 mL of 0.1 N HCl. Then the solution was filtered, diluted suitably and analyzed using UV/visible spectrophotometer at 280 nm.

On the other hand, 10 tablets weighed, triturated in a mortar. A ≡ 100 mg of acetyl salicylic acid was transferred to a 50 mL volumetric flask, diluted by 20 mL of diluting solution (acetonitrile and formic acid 99:1). The volumetric flask was shaken manually, centrifuged at 3000 rpm for 5 min and then the stock prepared was diluted. An aliquot of the diluted solution was injected into a liquid chromatograph with a detector set at 280 nm. The responses were compared with the standard to find the quantity in mg of acetyl salicylic acid present in the sample [31].

The chromatographic settings of clopidogrel besylate and acetyl salicylic acid content were summarized in Table-7.

TABLE-7
CHROMATOGRAPHIC CONDITIONS FOR THE ASSESSING CLOPIDOGREL BESYLATE AND ACETYL SALICYLIC ACID

Chromatographic conditions	Specification
Apparatus	HPLC
Column	C18, 250, 4.6, 5, (Inertsil)
Wavelength (nm)	240 (CB); 265 (ASA)
Detector	UV/PDA
Injection volume	20°
Flow rate	1.5 mL/min
Sample cooler temp	Ambient (25°C)
Run time	10 min
Elution	Isocratic

***in vitro* Dissolution studies:** The dissolution conditions for clopidogrel besylate as explained previously [32] (Table-8).

TABLE-6
CAPSULE FORMULATIONS

MTFC-1	MTFC-2	MTFC-3	MTFC-4	MTFC-5	MTFC-6	MTFC-7	MTFC-8	MTFC-9
CBM-1	CBM-2	CBM-3	CBM-4	CBM-5	CBM-6	CBM-7	CBM-8	CBM-9
ATM-1	ATM-2	ATM-3	ATM-4	ATM-5	ATM-6	ATM-7	ATM-8	ATM-9
ASM-1	ASM-2	ASM-3	ASM-4	ASM-5	ASM-6	ASM-7	ASM-8	ASM-9

TABLE-8
DISSOLUTION CONDITIONS FOR CLOPIDOGREL BESYLATE

Description	Clopidogrel besylate	ASA
Apparatus	Dissolution Apparatus USP Type II (Paddle)	
Medium	0.1 M HCl	0.1N HCl for 2h and then Phosphate buffer (pH 6.8) for next 45 min
Medium volume	900 mL	900 mL
Speed	50 rpm	100
Sampling intervals	5, 10, 20, 30, 45 and 60 min	30 min. 1 and 2h (in 0.1m HCl); 5, 10, 20, 30, 45 and 60 min (6.8 buffer)
Temperature	37 ± 0.5 °C	37 ± 0.5 °C

Kinetic treatment of the dissolution data: The dissolution data were further treated to find the best fit kinetic model and to know the possible release pattern [33-35].

RESULTS AND DISCUSSION

Thermal studies: Thermogram of clopidogrel besylate showed an endothermic peak at 175.95 ºC and combined with excipient showed a shift, which was observed with a peak of 171.17 °C (Fig. 1). On the other hand, thermogram of acetyl salicylic acid showed an endothermic peak at 134.18 ºC and combined with excipient showed a shift in thermogram was observed with a peak of 123.88 ºC (Fig. 2). This data confirms the impregnation of drugs with excipients used.

FTIR studies: The FTIR spectra revealed that the characteristic peaks and stretches of clopidogrel besylate were found even in the blend, indicates compatibility confirmations of clopidogrel besylate with excipients (Fig. 3). Similarly, the peaks and stretches of acetyl salicylic acid spectrum was found even in the blend (Fig. 4), indicates compatibility confirmations of acetyl salicylic acid with excipients.

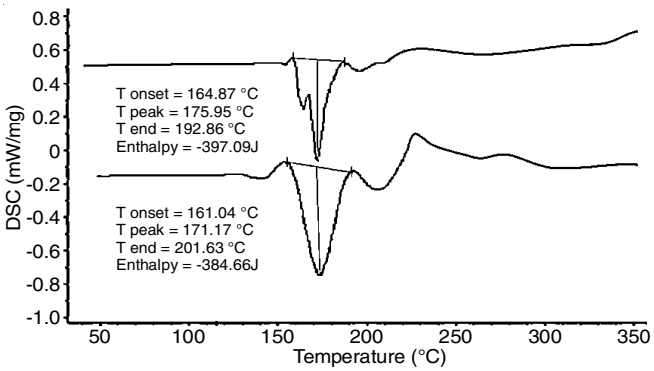

Fig. 1. DSC thermograms of clopidogrel besylate and blend

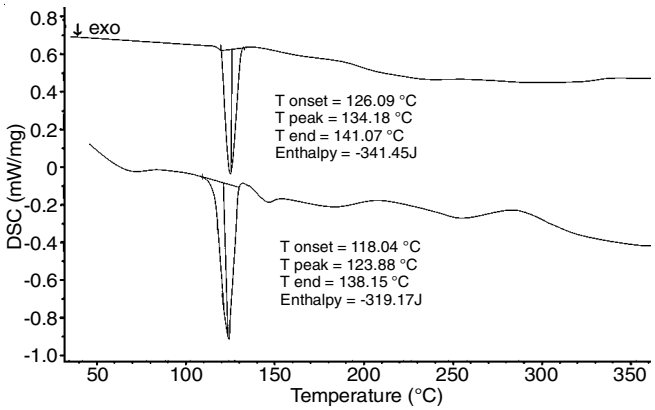

Fig. 2. DSC thermograms of acetyl salicylic acid and blend

Evaluation of parameters: Clopidogrel besylate blend showed an angle of repose, Carr's compressibility index and Hausner ratio values less than 30°, 10% and 1.25, respectively, which indicates the good flow properties (Table-9). Similarly, acetyl salicylic acid blend was also proved its good flow properties (Table-10).

The mini-tablets were subjected to various parameter assessments *viz*., uniformity of weight, hardness, thickness, friability and assay. The outcomes of these strictures exhibited nearly uniform thickness in all the formulations. The weights of all mini-tablets within the ± 7.5% (standard value for tablets weight ranged 80-250 mg) and passed the uniformity of weight as per official requests. All the tablets showed sufficient strength or hardness (> 4 Kg/cm^2), representing physical strength for which required during handling and transport. The hardness is not an absolute gauge of strength, so friability was also performed and the loss on friability was < 1% for all mini-tablets (acceptable limit). The conventional uncoated mini-tablets of clopidogrel besylate were disintegrated within 15 min (900

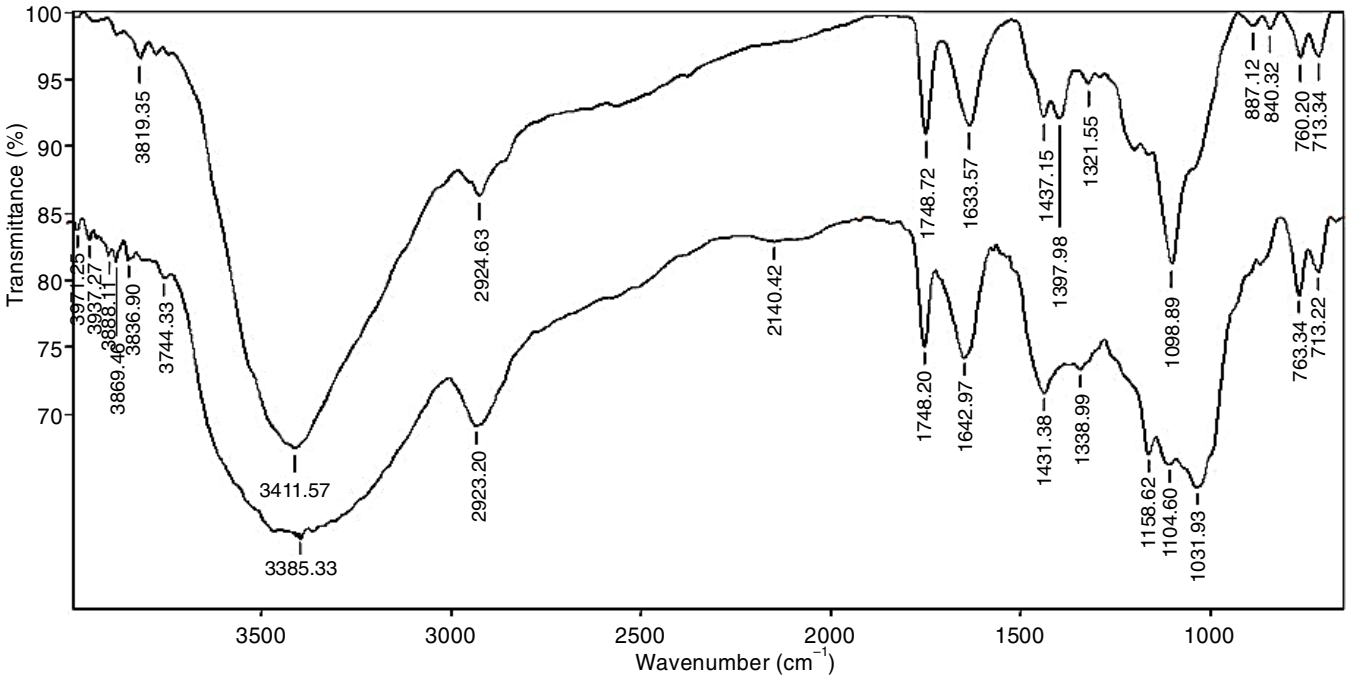

Fig. 3. FTIR spectra of clopidogrel besylate and its excipients

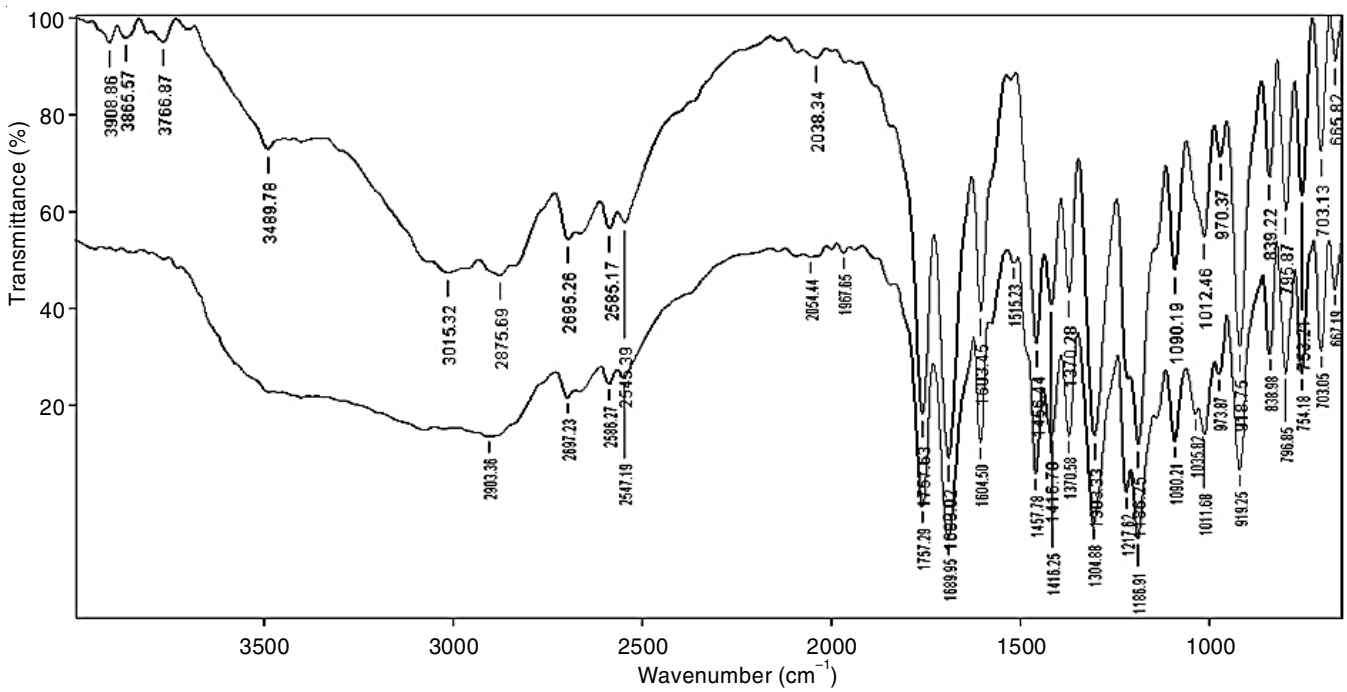

Fig. 4. FTIR spectra of acetyl salicylic acid and its excipients

TABLE-9
FLOW CHARACTER SPECIFICATIONS OF CLOPIDOGREL BESYLATE BLEND

Formulation	Angle of repose (°)	LBD	TBD	CI	HR
CBM-1	29.11 ± 0.02	0.364 ± 0.05	0.386 ± 0.01	5.683 ± 0.08	1.059 ± 0.02
CBM-2	28.17 ± 0.05	0.757 ± 0.07	0.788 ± 0.058	3.928 ± 0.02	1.040 ± 0.03
CBM-3	28.38 ± 0.01	0.526 ± 0.03	0.584 ± 0.02	9.588 ± 0.04	1.105 ± 0.04
CBM-4	28.84 ± 0.02	0.523 ± 0.03	0.565 ± 0.05	7.091 ± 0.02	1.077 ± 0.02
CBM-5	27.54 ± 0.07	0.451 ± 0.05	0.498 ± 0.02	9.235 ± 0.02	1.100 ± 0.01
CBM-6	30.21 ± 0.05	0.236 ± 0.04	0.256 ± 0.03	7.844 ± 0.04	1.084 ± 0.01
CBM-7	29.06 ± 0.01	0.254 ± 0.03	0.267 ± 0.02	5.222 ± 0.03	1.056 ± 0.03
CBM-8	29.16 ± 0.06	0.367 ± 0.02	0.388 ± 0.01	5.911 ± 0.02	1.061 ± 0.02
CBM-9	27.77 ± 0.08	0.267 ± 0.02	0.275 ± 0.01	2.188 ± 0.02	1.021 ± 0.02

Values in mean ± SD; trials (n = 3)

TABLE-10
FLOW CHARACTER SPECIFICATIONS OF ACETYL SALICYLIC ACID BLEND

Formulation	Angle of repose (°)	LBD	TBD	CI	HR
ASM-1	29.98 ± 0.05	0.259 ± 0.02	0.269 ± 0.03	3.732 ± 0.04	1.039 ± 0.01
ASM-2	29.05 ± 0.04	0.529 ± 0.04	0.537 ± 0.02	1.493 ± 0.02	1.016 ± 0.02
ASM-3	28.41 ± 0.02	0.569 ± 0.05	0.579 ± 0.06	1.731 ± 0.02	1.018 ± 0.01
ASM-4	28.19 ± 0.01	0.525 ± 0.02	0.546 ± 0.04	3.854 ± 0.02	1.041 ± 0.02
ASM-5	29.36 ± 0.02	0.452 ± 0.02	0.459 ± 0.01	1.525 ± 0.04	1.015 ± 0.03
ASM-6	28.52 ± 0.03	0.548 ± 0.02	0.556 ± 0.04	1.622 ± 0.05	1.017 ± 0.05
ASM-7	26.39 ± 0.02	0.256 ± 0.05	0.260 ± 0.02	1.931 ± 0.02	1.020 ± 0.02
ASM-8	28.25 ± 0.01	0.526 ± 0.01	0.542 ± 0.02	3.143 ± 0.03	1.033 ± 0.01
ASM-9	27.15 ± 0.02	0.660 ± 0.01	0.667 ± 0.02	1.202 ± 0.02	1.013 ± 0.02

Values in mean ± SD; trials (n = 3)

s), whereas the enteric coated mini-tablets of acetyl salicylic acid did not show any sign of disintegration in 0.1 M HCl for 2 h and disintegrated within 45 min (2700 s) in pH 6.8 buffer, which proves the enteric coating efficiency of acetyl salicylic acid enteric-coated mini-tablets. An appreciable uniformity in clopidogrel besylate and acetyl salicylic acid content were observed among different batches of mini-tablets and the percentage of drug content was more than 95% (Tables 11 and 12).

Dissolution studies: More than 75% of clopidogrel besylate was released within 60 min (uncoated) (Fig. 5). On the other hand, the enteric-coated mini-tablets of acetyl salicylic acid did not show any sign of dissolution in 0.1 M HCl for 2 h and > 75% dissolved within 45 min in pH 6.8 buffer (Fig. 6), which

TABLE-11
PHYSICAL CHARACTERISTICS OF CB MTs

Formulation	Uniformity of weight (mg)	Hardness (cm^2)	Thickness (mm)	Friability (%)	Disintegration (s)	Assay (%)
CBM-1	199.2 ± 2.31	5.9 ± 0.02	3.01 ± 0.01	0.41 ± 0.01	240 ± 5	95.73 ± 1.25
CBM-2	200.1 ± 1.51	6.8 ± 0.08	2.99 ± 0.02	0.34 ± 0.02	245 ± 7	98.09 ± 1.32
CBM-3	201.2 ± 1.35	7.1 ± 0.06	3.00 ± 0.01	0.42 ± 0.02	258 ± 8	99.39 ± 0.95
CBM-4	200.0 ± 2.26	8.3 ± 0.03	3.02 ± 0.01	0.29 ± 0.02	249 ± 3	98.02 ± 2.25
CBM-5	200.2 ± 1.98	5.7 ± 0.09	2.98 ± 0.01	0.37 ± 0.02	324 ± 9	98.77 ± 1.65
CBM-6	199.9 ± 1.57	7.2 ± 0.04	3.00 ± 0.02	0.15 ± 0.01	240 ± 7	97.94 ± 0.88
CBM-7	199.8 ± 1.64	5.3 ± 0.03	3.01 ± 0.01	0.14 ± 0.01	335 ± 6	98.58 ± 2.33
CBM-8	200.8 ± 1.08	5.1 ± 0.02	3.02 ± 0.01	0.31 ± 0.01	301 ± 4	97.48 ± 3.25
CBM-9	200.3 ± 2.06	7.2 ± 0.04	2.99 ± 0.01	0.11 ± 0.01	342 ± 2	98.51 ± 4.25

Values in mean ± SD; trials made (n = 3)

TABLE-12
PHYSICAL CHARACTERISTICS ASA MTs

Formulation	Uniformity of weight (mg)	Hardness (cm^2)	Thickness (mm)	Disintegration (s)		Assay (%)
				0.1 M HCl (2 h)	pH 6.8	
ASM-1	200.34 ± 1.09	5.7 ± 0.04	3.00 ± 0.02	0.00	356 ± 6	98.54 ± 1.65
ASM-2	201.20 ± 1.65	6.5 ± 0.02	3.01 ± 0.01	0.00	312 ± 8	98.02 ± 1.95
ASM-3	200.25 ± 1.73	7.1 ± 0.06	2.99 ± 0.02	0.00	369 ± 7	96.36 ± 2.48
ASM-4	201.98 ± 2.15	5.6 ± 0.05	3.01 ± 0.01	0.00	377 ± 5	99.25 ± 1.65
ASM-5	200.87 ± 1.46	8.2 ± 0.01	3.01 ± 0.02	0.00	333 ± 9	98.26 ± 1.66
ASM-6	200.58 ± 1.68	7.2 ± 0.02	3.00 ± 0.01	0.00	355 ± 8	98.85 ± 1.26
ASM-7	200.39 ± 1.84	6.9 ± 0.06	3.01 ± 0.02	0.00	381 ± 5	99.64 ± 2.22
ASM-8	199.32 ± 2.15	7.5 ± 0.07	3.00 ± 0.01	0.00	394 ± 6	98.16 ± 2.34
ASM-9	199.28 ± 3.12	6.8 ± 0.03	3.01 ± 0.01	0.00	365 ± 3	98.29 ± 2.36

Values in mean ± SD; trials made (n = 3)

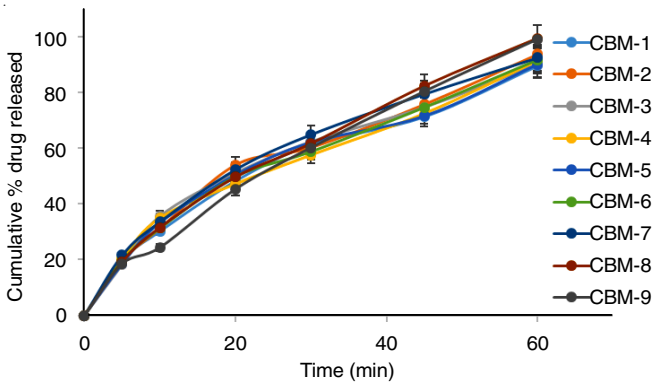

Fig. 5. Zero-order release plots for clopidogrel besylate mini tablets

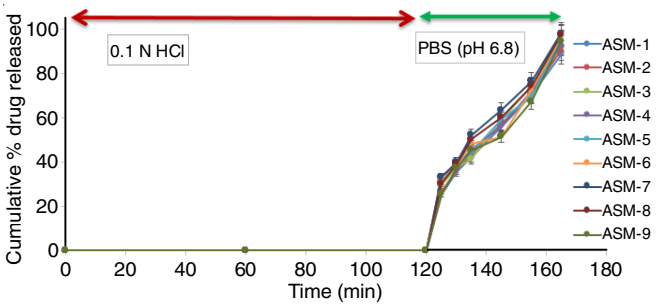

Fig. 6. Zero-order release plots for acetyl salicylic acid mini tablets

reveals the firmness of the enteric coat on mini-tablets of acetyl salicylic acid.

The mechanism of drug release from the formulations when tried to fit zero order, First order, Higuchi, Korsmeyer Peppa's and Hixon Crowell's plots. The regression and inter-pretation of release exponent value (n) were assessed and graphically represented in Figs. 7 and 8. Based on these data, it was confirmed Higuchi's model is best fit and the release was non-fickian for all clopidogrel besylate mini tablets, where as for acetyl salicylic acid formulations *i.e.*, ASM-4, ASM-5, ASM-6 and ASM-7 followed fickian and remaining acetyl salicylic acid formulations followed non-fickian release. The kinetic models of CB MTs are depicted in Table-13.

Conclusion

Distinct mini-tablets of uncoated clopidogrel besylate and enteric-coated acetyl salicylic acid were effectively filled in hard gelatin capsules. The recapped capsules after filling mini-tablets were sealed with a droplet of water. The gastric related adverse effects of drugs were contradicted by using *Plantago ovata* seed mucilage as a tablet binder (as it already proved for its gastric protective actions). Thus, mini-tablets filled capsules of clopidogrel besylate and acetyl salicylic acid for treating transient ischemic attack without any gastric issues.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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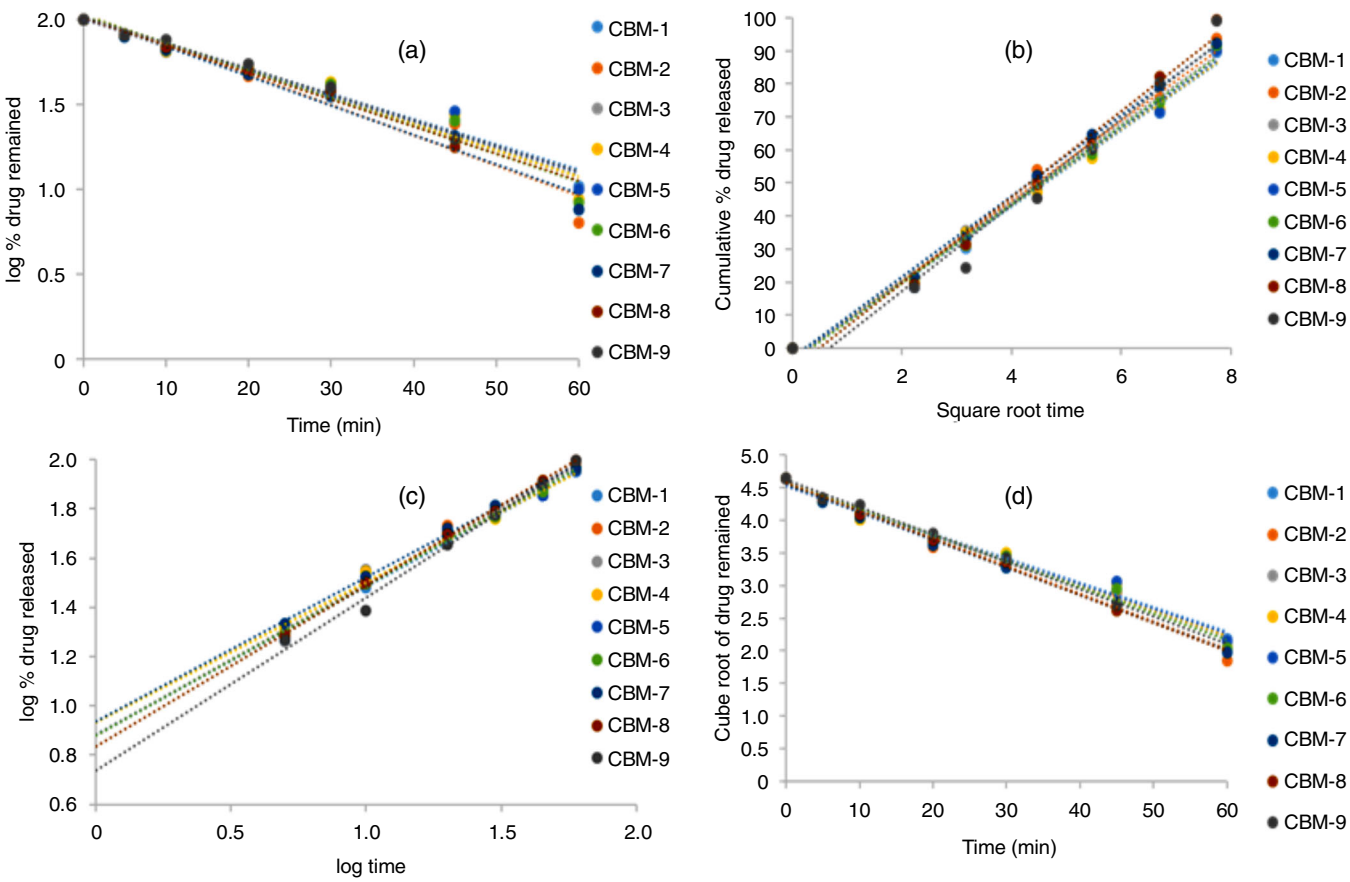

Fig. 7. Kinetic plots of CB MTs (a) First order (b) Higuchi (c) Korsmeyer Peppas (d) Hixson crewels

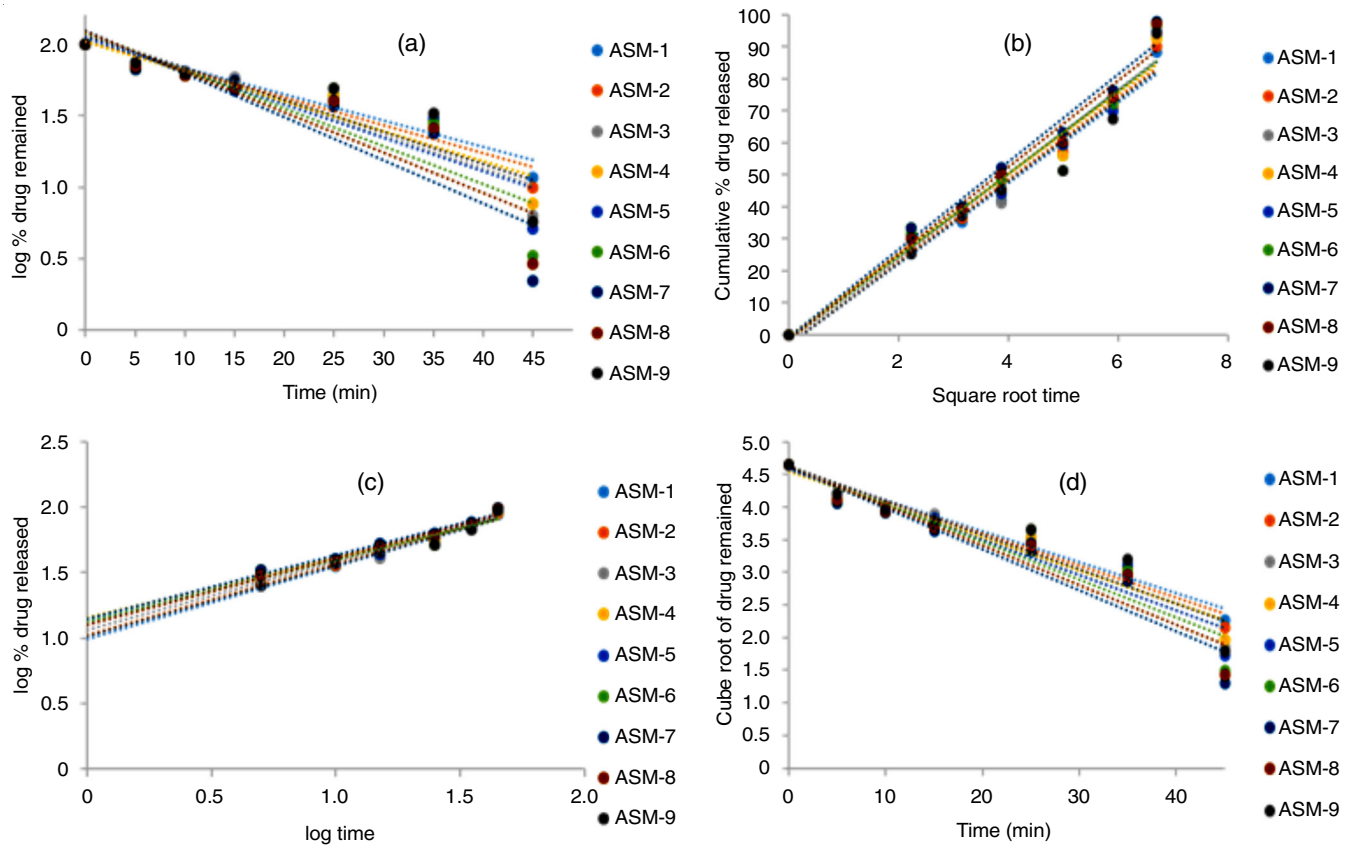

Fig. 8. Kinetic plots of ASA MTs (a) First order (b) Higuchi (c) Korsmeyer Peppas (d) Hixson crewels

TABLE-13
CORRELATION VALUES OF DRUG RELEASE FROM THE FORMULATIONS

Mini tablets	Code	Correlation (r^2)						Release type
		Zero order	First order	Higuchi	Hixson Crowell's	Korsmeyer Peppas	n	
Clopidogrel besylate	CBM-1	0.9424	0.9618	0.9917	0.9824	0.9960	0.5998	Non fickian
	CBM-2	0.9399	0.9363	0.9886	0.9763	0.9895	0.6163	Non fickian
	CBM-3	0.9257	0.9736	0.9927	0.9850	0.9771	0.6098	Non fickian
	CBM-4	0.9455	0.9392	0.9905	0.9739	0.9897	0.5695	Non fickian
	CBM-5	0.9299	0.9580	0.9908	0.9776	0.9848	0.6089	Non fickian
	CBM-6	0.9498	0.9537	0.9918	0.9840	0.9965	0.6071	Non fickian
	CBM-7	0.9325	0.9784	0.9965	0.9934	0.9972	0.5851	Non fickian
	CBM-8	0.9670	0.9851	0.9859	0.9463	0.9989	0.6525	Non fickian
	CBM-9	0.9813	0.9849	0.9709	0.9444	0.9892	0.7017	Non fickian
Acetyl salicylic acid	ASM-1	0.9560	0.9374	0.9827	0.9700	0.9866	0.5541	Non fickian
	ASM-2	0.9517	0.9241	0.9833	0.9640	0.9852	0.5409	Non fickian
	ASM-3	0.9522	0.8907	0.9747	0.9500	0.9574	0.5235	Non fickian
	ASM-4	0.9254	0.8836	0.9709	0.9352	0.9350	0.4545	Fickian
	ASM-5	0.9304	0.8319	0.9684	0.9096	0.9500	0.4800	Fickian
	ASM-6	0.9216	0.7856	0.9469	0.8778	0.9134	0.4762	Fickian
	ASM-7	0.9268	0.8130	0.9837	0.9164	0.9695	0.4813	Fickian
	ASM-8	0.9361	0.8144	0.9789	0.9121	0.9751	0.5090	Non fickian
	ASM-9	0.9373	0.8133	0.9513	0.8921	0.9554	0.5422	Non fickian

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