

## DEVELOPMENT AND EVALUATION OF ACENOCOUMAROL SUBLINGUAL TABLET

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### ABSTRACT:

**Objective:** The objective of the present investigation was to develop a formulation of Sublingual tablets of Acenocoumarol, having about 60% bioavailability orally due to first pass metabolism. **Materials and Method:** Sublingual tablets were prepared by various Super disintegrants like Croscarmellose Sodium (CCS), and Sodium Starch Glycolate (SSG) by direct compression method. The resultant batches were evaluated for precompression and post compression parameters like hardness, wetting time, in vitro disintegration time, drug content, and in vitro dissolution of the drug. **Results and Discussion:** The optimized formulation exhibiting a minimum disintegration time of  $18.3 \pm 0.59$  seconds, a wetting time of  $15.6 \pm 1.55$  seconds, and a drug release of 99.26 % in 10 minutes, outperforming the other nine batches. Stability studies of batch F9 showed no significant changes in hardness, wetting time, in vitro disintegration time, drug content, and *In vitro* dissolution profile over one month at  $40^\circ \pm 2^\circ \text{C}$  and  $75 \pm 5\%$  RH. The study concluded that sublingual tablets of Acenocoumarol can be successfully prepared by using the direct compression method, thereby improving patient compliance.

### INTRODUCTION:

Haemostasis is a vital physiological process responsible for preventing excessive blood loss following vascular injury and involves vascular spasm, platelet plug formation, and blood coagulation. Anticoagulant drugs are commonly prescribed for the prevention and treatment of thromboembolic disorders such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and transient ischemic attacks. Therefore, it is still an urgent problem to develop new hemostatic materials to effectively control bleeding and strive for the survival rate of severely injured patients.

Acenocoumarol is a coumarin derivative that acts as a vitamin K antagonist and inhibits the synthesis of vitamin K-dependent clotting factors. Although it is rapidly absorbed following oral administration, it undergoes extensive first pass hepatic metabolism, resulting in moderate oral bioavailability and delayed onset of action. Sublingual drug delivery is an effective alternative to conventional oral administration, as drugs are absorbed directly into the systemic circulation through the highly vascularized sublingual mucosa, bypassing hepatic metabolism. This route offers rapid onset of action, improved bioavailability, and enhanced patient compliance, particularly in emergency conditions and in patients with swallowing difficulties. Therefore, the present study was undertaken to formulate and evaluate sublingual tablets of Acenocoumarol with the aim of achieving rapid disintegration, faster drug release, and improved therapeutic efficacy.

**MATERIALS AND METHOD:**

**Materials:**

Acenocoumarol was procured from Torrent Pharmaceuticals Ltd. Croscarmellose sodium (CCS), sodium starch glycolate (SSG), microcrystalline cellulose (Avicel PH-102), mannitol, aspartame, magnesium stearate, and talc were procured from Chemco Industries, Gujarat, India.

**Fabrication of Sublingual Tablets<sup>5-15</sup>**

Sublingual tablets were prepared by the direct compression method. All ingredients were passed through sieve no. 60 and blended uniformly using geometric dilution. The prepared powder blends were compressed using a rotary tablet compression machine with flat-faced punches. The tablet weight was kept constant for all formulations (Table 1).

**Table 1: Formulation batches of Acenocoumarol sublingual tablet**

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acenocoumarol	6	6	6	6	6	6	6	6	6
Avicel pH 102	30	30	30	30	30	30	30	30	30
Croscarmellose Sodium	3.6	5.4	7.2	3.6	5.4	7.2	3.6	5.4	7.2
SSG	3.6	3.6	3.6	5.4	5.4	5.4	7.2	7.2	7.2
D-mannitol	69.6	67.8	66	67.8	66	64.2	66	64.2	62.4
Aspartame	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
SLS	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Talc	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
<b>Total weight</b>	<b>120</b>	<b>120</b>	<b>120</b>	<b>120</b>	<b>120</b>	<b>120</b>	<b>120</b>	<b>120</b>	<b>120</b>

**Determination of precompression parameters<sup>16-20</sup>**

Hausner's ratio, bulk density, tapered density, compressibility index, and angle of repose were all measured. Good flow qualities were indicated by the powder mixture's minimum Carr's index, Hausner's ratio, and angle of repose.

- **Bulk density:** Carefully weigh the powder mixture and transfer it to a measuring cylinder. Measure the volume of the powder without applying pressure. The volume is expressed as grams per millilitre (gm/ml).

$$\text{Bulk Density} = \frac{\text{Mass of powder (gm)}}{\text{Bulk Volume of powder (ml)}}$$

- **Tapped density:** The tapped density was determined by placing a graduated cylinder containing the formulation blend on a mechanical tapping apparatus. The volume was tapped until a constant tapped volume was achieved. Tapped density is expressed as grams per millilitre (gm/ml).

$$\text{Tapped Density} = \frac{\text{Mass of powder (gm)}}{\text{Tapped Volume of powder (ml)}}$$

- **Hausner's ratio:** Hausner's ratio, determined by dividing the tapped density by the bulk density of a powder, serves as an indicator of powder flow. A ratio at or below 1.25 signifies favourable flow properties, while a ratio surpassing 1.25 indicates inadequate flow.
- **Compressibility index:** The compressibility index is a percentage value obtained by calculating the difference between the tapped density and bulk density of a material, then dividing this difference by the tapped density. It serves as a measure of the compressibility or ability of a powder to decrease in volume under pressure.

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

- **Angle of repose:** Angle of repose was determined by funnel method. Powder blend was poured from funnel that can be raised vertically until it reaches maximum cone height (h) was obtained. Radius (r) of the pile was

measured. Angle of repose was measured by following formula.

$$\tan \theta = \frac{h}{r} \quad \theta = \tan^{-1} \frac{h}{r}$$

Where,  $\theta$  = Angle of repose,  $h$  = Height of pile,  $r$  = Radius of pile

#### Determination of post compression parameters<sup>16-20</sup>

- **Thickness and diameter:** Tablet thickness and diameter were determined using Digimatic Vernier calipers. 6 tablets were chosen, and their thickness and diameter were measured by positioning them between the 2 arms of the Vernier calipers.
- **Hardness:** Tablet hardness refers to the force necessary to fracture a tablet in a diametric compression trial. The crushing strength of tablets was assessed using a Monsanto-type hardness tester.
- **Weight variation:** Twenty tablets were randomly selected, and their collective weight was determined using an electronic balance to establish an average weight (Table 2).

Table 2: Weight variation limit

Average weight of tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250mg or more	±5

- **Friability test:** The friability of the tablets was assessed using a Roche-type friabilator. Initially, twenty tablets were weighed, then subjected to the friabilator's rotation at 25 rpm for 4 minutes. Afterward, the tablets were removed and weighed again. The acceptable loss in weight should not exceed 1%. The percentage friability was calculated using the provided equation.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

- **Drug content:** Ten tablets were pulverized, and an amount equivalent to 6 mg of Acenocoumarol was weighed and dissolved in 100 ml of phosphate buffer with a pH of 6.8. After filtration, 2 ml of the filtrate was diluted to 10 ml, and the absorbance of this solution was assessed using a UV spectrophotometer at a wavelength of 283 nm.
- **In Vitro Disintegration test:** The test involved using a digital tablet disintegration test apparatus to assess six tablets. Phosphate buffer with a pH of 6.8, maintained at a temperature of  $37 \pm 0.5$  °C, served as the disintegration media. The time taken, measured in seconds, was recorded for the tablets to completely disintegrate, leaving no residue in the apparatus.
- **In Vitro Drug release study:** The percentage of drug release from Acenocoumarol sublingual tablets was assessed using the USP type II dissolution apparatus, operating at 50 rpm and maintained at  $37 \pm 0.5$  °C with 900 ml of phosphate buffer (pH 6.8). Samples were withdrawn at regular intervals, replaced with fresh dissolution media, and filtered through a 0.45 $\mu$ m membrane filter. The absorbance of these samples was analyzed using a UV at a wavelength of 283 nm.
- **Stability study of optimized batch:** The study conducted a stability assessment of the optimized batch over one month under conditions of  $40^\circ\text{C} \pm 2^\circ\text{C}$  and  $75\% \pm 5\%$  RH, adhering to ICH guidelines for accelerated stability testing. The tablets were wrapped in aluminum foil to shield them from light exposure. After 30 days, the tablets underwent evaluation for hardness, friability, drug content, wetting time, *in vitro* disintegration time, and *in vitro* drug release.

## RESULT:

### Determination of Melting point of Acenocoumarol:

Melting point determination, a commonly employed technique for drug identification, was conducted using a melting point apparatus, revealing a range of 194 to 201 °C for Acenocoumarol. This falls within the reported melting point range of 196 to 199 °C for drug. Consequently, it was inferred that the provided substance is indeed Acenocoumarol (Table 3).

**Table 3: Melting point of Acenocoumarol**

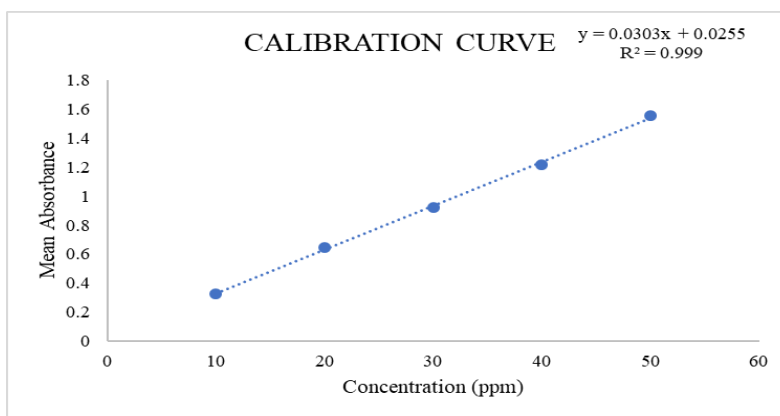
Sr. No.	Reported Melting Point (°C)	Observed Melting point (°C)
1.	196 to 199 °C	195 to 198 °C
2.		197 to 201 °C
3.		194 to 197 °C

**Estimation of Drug by UV Spectrophotometric Method:**

UV spectrophotometric analysis of Acenocoumarol was carried out in phosphate buffer at pH 6.8. The drug showed maximum absorbance ( $\lambda_{max}$ ) at 283 nm. Calibration curve was constructed by plotting concentration versus absorbance, which showed good linearity over the concentration range of 10–50 ppm (Table 4 and Figure 1).

**Table 4: Absorbance of different concentration of Acenocoumarol in phosphate buffer at pH 6.8**

Sr. No.	Concentration (ppm)	Absorbance			Mean Absorbance $\pm$ S.D.
		I	II	III	
1	10	0.324	0.329	0.329	0.327 $\pm$ 0.0028
2	20	0.600	0.650	0.685	0.645 $\pm$ 0.0026
3	30	0.900	0.920	0.955	0.925 $\pm$ 0.0015
4	40	1.100	1.200	1.360	1.220 $\pm$ 0.0023
5	50	1.556	1.554	1.552	1.554 $\pm$ 0.0020



**Figure 1: Calibration curve of Acenocoumarol in phosphate buffer at pH 6.8**

**Precompression Parameters:**

The powder blend's bulk density, taped density, Hausner's ratio, Carr's index, and angle of repose were all measured. It was discovered that every parameter had acceptable flow characteristics. The tapped density ranged from  $0.62 \pm 0.663$  to  $0.70 \pm 0.743$  gm/ml, while the bulk density was found to be between  $0.53 \pm 0.549$  to  $0.57 \pm 0.589$  gm/ml. Carr's compressibility index was computed using the two data points mentioned above. The range of the compressibility index was  $11.11 \pm 13.29$  to  $18.57 \pm 20.75$ . Data on compressibility and flow ability showed that all powder mixes had adequate flow characteristics. Angle of repose also demonstrated the superior flow characteristics of all powder blends. The angle of repose was range of  $27.58 \pm 0.57$  to  $29.52 \pm 0.67$  so it indicates good flow property (Table 5).

**Table 5: Precompression Parameters**

Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio	Angle of repose (°)
F1	$0.56 \pm 0.579$	$0.66 \pm 0.703$	$15.15 \pm 17.33$	$1.17 \pm 1.201$	$27.75 \pm 0.27$
F2	$0.57 \pm 0.589$	$0.70 \pm 0.743$	$18.57 \pm 20.75$	$1.22 \pm 1.251$	$28.07 \pm 0.34$
F3	$0.57 \pm 0.589$	$0.68 \pm 0.723$	$16.17 \pm 18.35$	$1.19 \pm 1.221$	$28.39 \pm 0.50$
F4	$0.53 \pm 0.549$	$0.63 \pm 0.664$	$15.87 \pm 18.05$	$1.18 \pm 1.211$	$28.72 \pm 0.37$
F5	$0.54 \pm 0.559$	$0.65 \pm 0.693$	$16.92 \pm 19.10$	$1.20 \pm 1.231$	$27.58 \pm 0.57$
F6	$0.53 \pm 0.549$	$0.62 \pm 0.663$	$14.51 \pm 16.69$	$1.16 \pm 1.191$	$28.19 \pm 0.53$
F7	$0.56 \pm 0.579$	$0.65 \pm 0.693$	$13.84 \pm 16.02$	$1.16 \pm 1.191$	$29.52 \pm 0.67$

<b>F8</b>	0.53 ± 0.549	0.62 ± 0.663	14.51 ± 16.69	1.16 ± 1.191	28.19 ± 0.45
<b>F9</b>	0.56 ± 0.579	0.63 ± 0.664	11.11 ± 13.29	1.12 ± 1.151	28.68 ± 0.36

**Post compression parameters:**

Physical characteristics such as thickness, diameter, weight variation, hardness and friability were measured. It was discovered that The formulated batch's friability was 0.35% to 0.76%. The Formulated batch's thickness was found to be between 2.95 ± 0.046 to 3.13 ± 0.062. The Formulated batch's diameter was found to be between 5.97 ± 0.063 to 6.10 ± 0.004. The Formulated batch's hardness was found to be between 2.38 ± 0.20 to 3.07 ± 0.14. This was enough to keep the tablet from shattering while being transported. The Formulated batch's weight variation was 119.4 ± 1.23 to 121.9 ± 1.50, in accordance with the Indian Pharmacopeia (Table 6).

Wetting time of the formulated batches ranged from 15.6 ± 1.55 seconds to 38.2 ± 1.75 seconds. Batch F9, containing a combination of 7.2 mg CCS and 7.2 mg SSG, exhibited the shortest wetting time of 15.6 ± 1.55 seconds compared to the other batches. The In Vitro Disintegration time of the formulated batches ranged from 18.3 ± 0.59 seconds to 41.6 ± 0.59 seconds. Batch F9, containing a combination of 7.2 mg CCS and 7.2 mg SSG, exhibited the shortest In Vitro Disintegration time of 18.3 ± 0.59 seconds compared to the other batches. The drug content of the tablets prepared using the direct compression method ranged from 98.09% to 99.82%. These findings regarding drug content suggest that the sublingual tablet exhibited consistent distribution and accurate dosage of the active ingredient (Table 7).

**Table 6: Post compression parameters of Acenocoumarol Sublingual tablets**

Batch	Thickness (mm ± S.D.)	Diameter (mm ± S.D.)	Weight variation (mg ± S.D.)	Hardness (kg/cm <sup>2</sup> ± S.D.)	Friability (%)
<b>F1</b>	3.09 ± 0.015	6.00 ± 0.012	120.2 ± 1.37	2.97 ± 0.07	0.36
<b>F2</b>	3.13 ± 0.063	5.97 ± 0.064	120.2 ± 1.48	3.03 ± 0.20	0.53
<b>F3</b>	2.96 ± 0.120	6.10 ± 0.004	119.4 ± 1.23	2.90 ± 0.15	0.59
<b>F4</b>	2.95 ± 0.046	6.10 ± 0.004	121.5 ± 1.56	2.63 ± 0.17	0.76
<b>F5</b>	3.08 ± 0.037	5.97 ± 0.063	120.3 ± 1.49	2.90 ± 0.39	0.44
<b>F6</b>	3.13 ± 0.062	5.93 ± 0.064	121.9 ± 1.50	3.07 ± 0.14	0.52
<b>F7</b>	3.07 ± 0.117	6.03 ± 0.064	119.7 ± 1.85	2.60 ± 0.28	0.35
<b>F8</b>	2.96 ± 0.023	6.00 ± 0.012	120.9 ± 1.37	2.87 ± 0.25	0.75
<b>F9</b>	3.07 ± 0.059	6.03 ± 0.015	120.7 ± 1.53	2.38 ± 0.20	0.42

**Table 7: Wetting time, In Vitro disintegration time and Drug Content**

Batch	Wetting time (sec. ± S.D.)	In Vitro disintegration time (sec. ± S.D.)	Drug content (%)
<b>F1</b>	38.2 ± 1.75	41.6 ± 0.59	99.55
<b>F2</b>	35.6 ± 1.56	36.3 ± 0.59	99.01
<b>F3</b>	22.3 ± 2.55	27.3 ± 1.76	98.55
<b>F4</b>	31.8 ± 2.02	33.6 ± 1.55	99.06
<b>F5</b>	28.4 ± 0.02	32.6 ± 1.56	98.09
<b>F6</b>	20.2 ± 1.75	25.3 ± 1.55	99.06
<b>F7</b>	25.3 ± 0.60	31.6 ± 2.09	98.22
<b>F8</b>	18.6 ± 1.55	23.3 ± 1.17	97.08
<b>F9</b>	15.6 ± 1.55	18.3 ± 0.59	99.82

**In Vitro Drug Release study:**

The In Vitro Drug Release study was conducted using a dissolution test apparatus type II (paddle) in 900 ml of phosphate buffer at pH 6.8 as the dissolution medium at 37° ± 0.5 °C and 50 rpm. The results presented in Table 6.9 demonstrate that an increase in the concentration of the superdisintegrant correlates with enhanced drug release from the tablet. For formulations A1 to A4, the drug release was found to be 18.32 %, 19.32 %, 20.05 % & 24.09 % at 2 minutes respectively, reaching to 97.39 %, 98.09 %, 97.88 % and 98.09%, respectively by the end of 22, 22, 20 & 18 minutes. Similarly, formulations A5 to A8, the drug release was found to be 16.86 %, 19.06 %, 21.23 % & 22.55 % at 2 minutes respectively, reaching to 99.34 %, 98.73 %, 97.27 % & 98.88 %, respectively by the end of 22, 20, 18 & 16 minutes. Moreover, formulations A9 to A12, the drug release was found to be 19.69 %, 22.15 %, 25.49 % & 27.82 % at 2 minutes respectively, reaching to 99.62 %, 99.26 %, 97.67 % & 99.69 %, respectively by the end of 20, 18, 16 & 16 minutes respectively. The drug release profile illustrates that as the concentration of the

superdisintegrant increases, the *In Vitro* Drug Release profile also intensifies, as depicted in the figures above (Figure 2, 3 and 4).

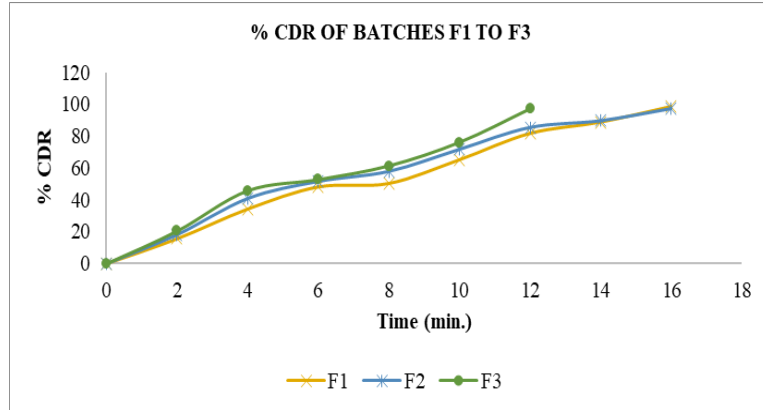


Figure 2: In-vitro drug release of Batches F1 to F3

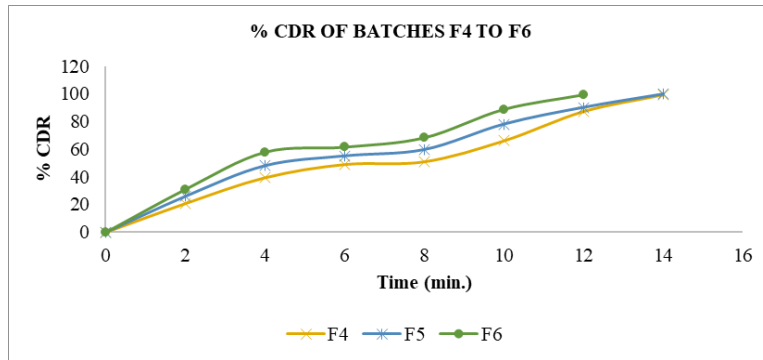


Figure 3: In-vitro drug release of Batches F4 to F6

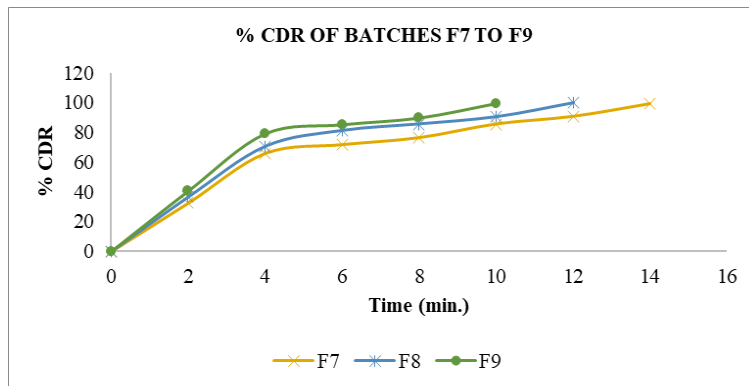


Figure 4: In-vitro drug release of Batches F7 to F9

**Stability study**

Based on the evaluation of various parameters, batch F9 was identified as the optimized batch due to its excellent surface appearance, mechanical strength, and drug content. It demonstrated a 99.26% drug release within 10 minutes, with a wetting time of 15.6 seconds and an *in vitro* disintegration time of 18.3 seconds, the shortest among all batches. Consequently, batch F9 was selected as the optimized batch. A stability study was conducted on the optimized batch at  $40 \pm 2$  °C and  $75 \pm 5$  % RH for one month. After this period, assessments of hardness, wetting time, *in vitro* disintegration time, and *in vitro* drug release were performed. The results, detailed in Tables 8 and 9,

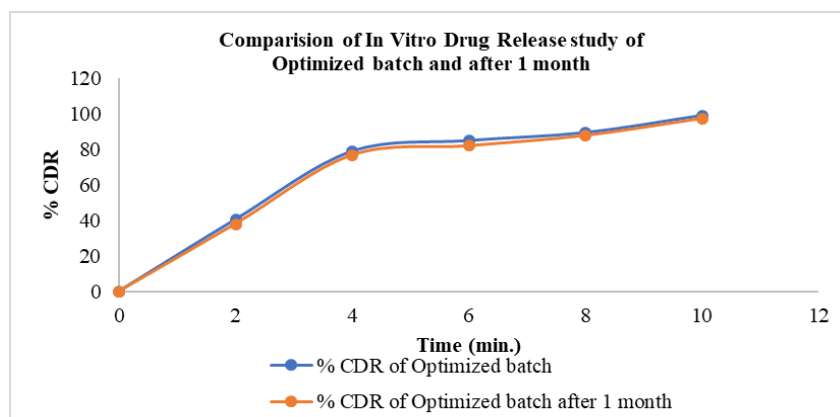
indicated no significant changes in these parameters, confirming the formulation's stability over time. A comparative study between the initial and post-stability results of the optimized batch is visually represented in Figure 5.

**Table 8: Result of the Stability study**

Sr. No.	Evaluation parameter	Results of optimized batch F9	Result after 1 month at 40° ± 2 °C and 75 ± 5 % RH
1	Hardness	2.38 ± 0.20 kg/cm <sup>2</sup>	2.12 ± 0.32 kg/cm <sup>2</sup>
2	Wetting Time	15.6 ± 1.55 sec.	20.3 ± 0.59 sec.
3	<i>In Vitro</i> Disintegration Time	18.3 ± 0.59 sec.	21 ± 0.67 sec.
4	Drug Content	99.82 %	98.35 %

**Table 9: *In Vitro* Drug Release Study of Stability Batch**

Time (Min.)	% CDR of Optimized Batch F9 (%)	% CDR of batch F9 After Time Period of 1 Month (%)
0	0	0
2	40.55	38.08
4	78.98	76.92
6	85.09	82.17
8	89.57	87.99
10	99.26	97.61



**Figure 5: Comparison of *In Vitro* Drug Release study of Optimized batch and Stability batch**

**CONCLUSION:**

Acenocoumarol is an anticoagulant drug used in the prevention of thromboembolic diseases in infarction and transient ischemic attacks, Acenocoumarol Rapidly absorbed orally with greater than 60% bioavailability. Sublingual tablets of Acenocoumarol were prepared by direct compression using two Superdisintegrants like CCS and SSG. All precompression parameters like Carr's Index, Hausner's Ratio and Angle of Repose meets the standard values of powder indicating good flow properties. The average weight, friability and hardness were within compendial limits which showed that all formulations possessed good mechanical strength. Drug content uniformity was within acceptable limits, which indicates a homogeneous distribution of drug in tablets. On the basis of various precompression and post compression parameters. The formulation F9 was optimized from the disintegration time of 18.3 ± 0.59 secs, wetting time 15.6 ± 1.55 secs and drug release of 99.26 % in 10 mins among all other nine batches of tablets. F9 batch contains CCS and SSG 6%. Thus, Batch F9 of Sublingual tablet was selected as an optimized batch by using desirability function. The results were found in good agreement and evaluated for further parameters like stability study. The result of stability study of the batch F9 showed that there was no significant change in Hardness, wetting time, *In-vitro* Disintegration time, Drug content, and *In Vitro* dissolution profile for a period of one month when stored at 40° ± 2 °C and 75 ± 5 % RH. From the study it was concluded that Sublingual tablet of Acenocoumarol can be successfully prepared using combination of Superdisintegrants by Direct compression method, which can provide rapid drug release within a short period time.

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**CONFLICT OF INTEREST:**

The authors declare that there is no conflict of interest.

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