

FORMULATION, DEVELOPMENT, AND EVALUATION OF IMMEDIATE-RELEASE CAFFEINE ANHYDROUS CAPSULES (100 MG)

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Article Info:

Received: 05 July 2026,

Revised: 23 August 2026,

Accepted: 13 September 2026

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DOI: <https://doi.org/10.5281/zenodo.22847919>



Citation:

Kavya S. U.^{1*}, Narasinga Rao U. H.¹, Annapoorna T.¹, Rohan Ahmmmod, S. Umme Shifa, Prashant H. K. (2026). Formulation, Development, And Evaluation Of Immediate-Release Caffeine Anhydrous Capsules (100 mg). International Journal of Clinical and Pharmaceutical Innovations, 1(6), 273-280.

ABSTRACT

The aim of this study is to formulate, develop, and evaluate immediate-release capsules containing 100 mg of Caffeine Anhydrous. Three different formulations (F1, F2, F3) were developed using the wet granulation technique. These formulations were developed to compare the influence of different diluent-based excipient matrices (specifically Mannitol, Lactose Monohydrate, and Dicalcium Phosphate) on drug release profiles. Pre-filling evaluations of the prepared granules of all batches showed excellent micromeritic flow properties, with Carr's index ranging from 5.71% to 9.72% and angle of repose between 21.94° and 22.44°. The prepared granules were filled into size-0 hard gelatin capsules. All formulations successfully passed the acceptable limits for weight variation, locking length, and content uniformity. In-vitro disintegration times were also rapid, occurring within 2 to 6 minutes. In-vitro dissolution studies were conducted in a pH 1.2 buffer as the dissolution medium. Formulation F1 (Mannitol-based) exhibited the most rapid and complete drug release compared to F2 and F3. Microbial content testing confirmed that F1 is microbiologically safe. Therefore, the wet granulation method successfully produced immediate-release caffeine capsules.

KEYWORDS: Caffeine Anhydrous, Immediate Release, Wet Granulation, Hard Gelatin Capsules, Excipient Matrix, Dissolution Profile.

INTRODUCTION

Oral drug delivery system is one of the most preferred routes of drug administration for new and existing formulations due to its ease of administration and also high patient compliance.^[1] The word capsule is derived from the Latin word "Capsula". Capsules are unit solid dosage forms enclosed in small gelatin shells. Capsules are mostly favoured because they are tasteless, odourless, and therapeutically inert, allowing for effortless medicament release in gastrointestinal fluids.^[2,3,4]

Caffeine is a purine alkaloid with the chemical formula $C_8H_{10}N_4O_2$ and, in pure form, it appears as a white

powder with a slightly bitter taste.^[5] It is among the most widely consumed central nervous system stimulants worldwide, and its stimulant effects are primarily mediated by adenosine receptor antagonism, which promotes alertness and wakefulness.^[6,7]

Pharmacokinetically, caffeine exhibits nearly 100% oral bioavailability, reaching peak plasma concentration within 30 to 60 minutes post-ingestion. Caffeine is primarily metabolized in the liver via the cytochrome P450 CYP1A2 isozyme into paraxanthine, theobromine, and theophylline. It has a half-life of 4 to 5 hours.^[8]

Immediate-release formulations are specifically designed to release the active pharmaceutical ingredient (API) rapidly upon administration, ensuring a quick onset of action.^[9] The selection of diluents and superdisintegrants is very critical in these formulations, as highly porous excipients govern the water-absorption capacity of the solid unit dosage form.^[10,11]

Previous studies by Alam K. et al.^[12] and Palma A.S.A. et al.^[13] demonstrated the efficacy of optimizing filler-binders and polymers in both direct compression and wet granulation of caffeine. Hjaltason E.M. et al.^[14] established that superdisintegrant concentration strictly modulates initial burst release. Furthermore, Al-Ragawi A.A.M.M.^[15] emphasized the necessity of excipient-drug compatibility screening to prevent physical degradation.

MATERIALS AND METHODS

1. Materials: Pharma-grade materials were utilized for all formulations.

- **Active Pharmaceutical Ingredient:** Caffeine Anhydrous (Nice Chemicals Pvt. Ltd.).
- **Diluents/Fillers:** Mannitol (SD Fine-Chem Limited), Microcrystalline Cellulose (Yarrow Chem Products), Lactose Monohydrate (SD Fine-Chem Limited), Calcium Phosphate Dibasic Dihydrate (Rolex Chemical Industries).
- **Superdisintegrant:** Sodium Starch Glycolate (SD Fine-Chem Limited).
- **Binders:** PVP-K30 and Potato Starch (SD Fine-Chem Limited).
- **Glidant & Lubricant:** Talc (Rolex Chemical Industries) and Magnesium Stearate (SD Fine-Chem Limited).

2. Determination of Melting Point

The melting point of Caffeine Anhydrous was determined using a digital melting point apparatus (Analab Scientific Instruments Pvt. Ltd.) via the capillary method. The capillary tube was sealed at one end and then filled with a small quantity of the pure drug. The prepared tube is then inserted into the mineral oil phase. The temperature at which the powder began to melt was recorded.^[16] The acceptable literature range for melting point of Caffeine Anhydrous is 235-239°C.^[17]

3. Standard Calibration Curve

a) Preparation of reagents^[16]

- 0.2M KCl is prepared by dissolving 14.911 g of Potassium Chloride in 1000 mL distilled water.

- 0.2M HCl is prepared by mixing 7.292 g (~16.3 mL) of Hydrogen Chloride in 1000 mL distilled water.
- 0.2M KH_2PO_4 is prepared by dissolving 27.218 g of Potassium Dihydrogen Phosphate in 1000 mL distilled water.
- 0.2M NaOH is prepared by dissolving 8.0 g of Sodium Hydroxide in 1000 mL distilled water.

b) Preparation of buffer^[16]

- **HCl buffer (pH 1.2):** 50 mL of 0.2M KCl is taken in a 200 mL volumetric flask, and 85 mL of 0.2M HCl is added. Add distilled water to make up the volume to 200 mL.
- **Phosphate buffer (pH 7.4):** 50 mL of 0.2M KH_2PO_4 is taken in a 200 mL volumetric flask, and 39.1 mL of 0.2M NaOH is added. Add distilled water to make up the volume to 200 mL.

c) Determination of UV Absorbance

Standard solutions containing 5, 10, 15 and 20, µg/mL of Caffeine Anhydrous were prepared in pH 1.2 HCl buffer and pH 7.4 phosphate buffers. The UV absorbance of each sample was measured using a Shimadzu UV-1800 Spectrophotometer against a blank pH buffer at 272 nm (pH 1.2) and 273 nm (pH 7.4).

4. Development of Formulations

Immediate-release capsules were prepared by the wet granulation method targeting a granules weight of 400 mg to be filled in per capsule.

- **Formulation 1 (F1 – Mannitol):** Caffeine anhydrous, Mannitol, Sodium starch glycolate, and PVP-K30 (powder) were homogeneously dry-mixed. The solvent (purified water) was added to form a damp mass.
- **Formulation 2 (F2 - Lactose):** Caffeine anhydrous, Microcrystalline cellulose, and Lactose monohydrate were mixed. A translucent paste of potato starch (prepared by cooking starch powder with purified water) was used as the binder.
- **Formulation 3 (F3 - DCP):** Caffeine anhydrous, Microcrystalline cellulose, Calcium phosphate dibasic dihydrate, and Sodium starch glycolate were mixed and bound with potato starch paste.

Table 1: Amount of Drug and Excipients Used Per Capsule.

Sl. No.	Drug and Excipients	F1	F2	F3
01	Caffeine anhydrous	100 mg	100 mg	100 mg
02	Mannitol	272 mg	-	-
03	Microcrystalline cellulose	-	120 mg	124 mg
04	Lactose monohydrate	-	156 mg	-
05	Calcium phosphate, Dibasic dihydrate	-	-	140 mg
06	Sodium starch glycolate	20 mg	-	12 mg
07	PVP-K30	4 mg	-	-

08	Starch (potato)	-	16 mg	16 mg
09	Talc	2 mg	4 mg	4 mg
10	Magnesium stearate	2 mg	4 mg	4 mg
11	TOTAL	400 mg	400 mg	400 mg

All these powder mixtures were converted into damp mass. The damp masses were then passed through sieve no-10, dried in a hot air oven at 60°C for 30 minutes, and then again dry-sieved through sieve no-22 to obtain uniform and smaller particle size. The granules were lubricated with Talc and Magnesium stearate for exactly 3 minutes to enhance flow properties. Overmixing may form a hydrophobic layer covering the granules, which may affect dissolution profile and disintegration time. Granules were filled into size-0 hard gelatin capsule shells and locked properly.

5. Pre-filling Parameters of Granules^[18, 19]

- a) **Bulk Density:** A 5 g sample of granules was introduced into a 10 mL graduated measuring cylinder without compaction. Bulk density was calculated using the formula:

$$\text{Bulk Density} = \frac{\text{Total mass of granule}}{\text{Bulk volume of granules}}$$

- b) **Tapped Density:** The 5 g sample in the measuring cylinder was tapped 200 times from a height of approximately 1.5 cm. Tapped density was calculated using the formula:

$$\text{Tapped Density} = \frac{\text{Total mass of granule}}{\text{Tapped volume of granules}}$$

- c) **Carr's Compressibility Index and Hausner's Ratio:** Flowability was indirectly measured using Carr's Index and Hausner's Ratio formulas derived from bulk and tapped densities. The acceptable scale of flowability is detailed in Table 2.

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 2: Scale of Flowability for Carr's Compressibility Index and Hausner's Ratio.

Carr's index (%)	Hausner's ratio	Flowability
5-15	1.05-1.18	Excellent
12-16	1.14-1.20	Good
18-21	1.22-1.26	Fair-passable
23-25	1.30-1.54	Poor
33-38	1.50-1.61	Very poor
>40	>1.67	Very, very poor

- d) **Angle of Repose:** The fixed funnel method was used to measure angle of repose. Granules were poured through a funnel fixed at a certain height

above a horizontal surface. The angle of repose was calculated using the pile's height and the base radius. The acceptable scale used is detailed in Table 3.

Table 3: Relationship Between Angle of Repose And Flowability.

Angle of repose	Flowability
<25	Excellent
25-30	Good
30-40	Moderate
>40	Poor

6. Post-filling Parameters of Capsules

- a) **Locking Length:** The closed length of the filled capsules was measured using a Mitutoyo Digital Vernier Caliper to ensure compliance with reported literature limit (~21.6 mm) to prevent content leakage during packing, handling and transportation.^[16,20]

- b) **Weight Variation:** Twenty randomly selected capsules were individually weighed to calculate the average weight. Compliance was determined based on IP limits. The test is considered passed if not more than two individual weights deviated by more than ±7.5% from the average.^[16]

- c) **Content Uniformity:** Ten capsules were randomly selected, weighed, and powdered individually. The powder obtained from each capsule was separately triturated using mortar-pestle to break down the granules. The obtained powder is then mixed with 100 mL of pH 1.2 buffers, and then again diluted to obtain sample of concentration 10 µg/mL. The prepared sample is then analyzed spectrophotometrically at 272 nm. The batch complies with IP standards, if 0 units fall outside the range of 75% to 125%.^[16]

- d) **In-Vitro Disintegration Test:** This test was conducted using a basket rack assembly

disintegration apparatus containing liquid medium (water) maintained at $37 \pm 2^\circ\text{C}$. Six capsules per formulation were tested to measure the mean time for complete shell rupture and disintegration.^[16]

- e) **In-Vitro Dissolution Studies:** Testing was performed using a USP dissolution test apparatus (basket type) containing 900 mL of 0.1N HCl (pH 1.2 buffer) maintained at $37 \pm 0.5^\circ\text{C}$ at 75 rpm with 6 capsules from each formulation. Samples (5 mL) were withdrawn at 10, 20, 30, and 40-minute intervals, filtered if required and then diluted to obtain sample concentration of 5, 10, 15 and 20 $\mu\text{g/mL}$. These samples are then analyzed spectrophotometrically at 272 nm.^[17] After each withdrawal of 5 mL sample, another 5 mL buffer was immediately introduced to the apparatus bowl to keep up the volume maintained at 900 mL throughout the test.

- f) **Microbial Content Test:** F1 was examined via a validated plate-count procedure. Samples were plated on Soybean-Casein Digest Agar (SCDA) molten medium alongside positive control and negative control. The prepared plates were incubated at 37°C for 48 hours.

RESULTS AND DISCUSSION

1. Preformulation results

Caffeine Anhydrous is an odourless, bitter, and white to creamy white crystalline powder. The melting point was determined to be 238°C , which falls within the reported literature range of $235\text{--}239^\circ\text{C}$. The standard calibration curves in both pH 1.2 and pH 7.4 buffers demonstrated good linearity in the 5–20 $\mu\text{g/mL}$ concentration range, giving regression (R^2) values of 0.9995 and 0.9994, respectively as shown in Figure 1 and Figure 2.

Table 4: Data of Standard Curve of Caffeine Anhydrous In Ph 1.2 and Ph 7.4 Buffer.

Sl. No.	Concentration ($\mu\text{g/mL}$)	Absorbance at 272 nm (pH 1.2)	Absorbance at 273 nm (pH 7.4)
1	0	0	0
2	5	0.230	0.222
3	10	0.454	0.456
4	15	0.712	0.710
5	20	0.942	0.952

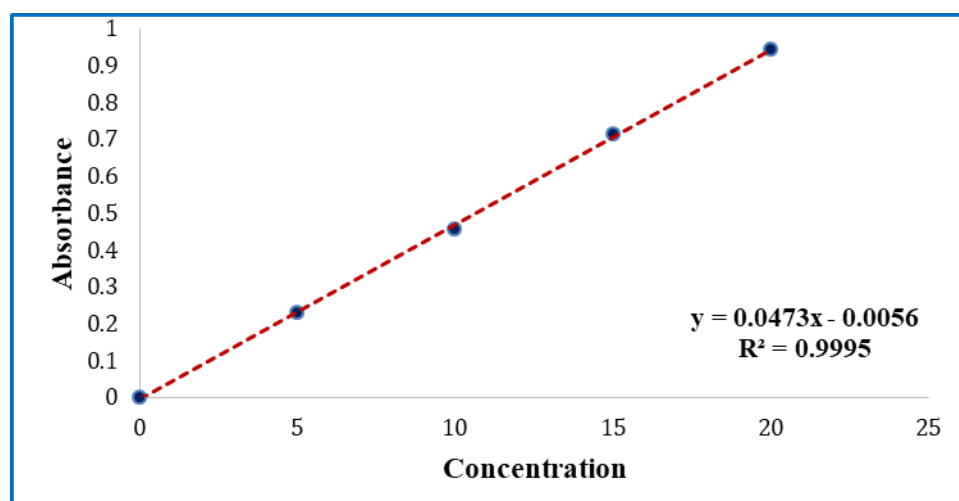


Figure 1: Standard calibration curve of Caffeine Anhydrous for pH 1.2 buffer.

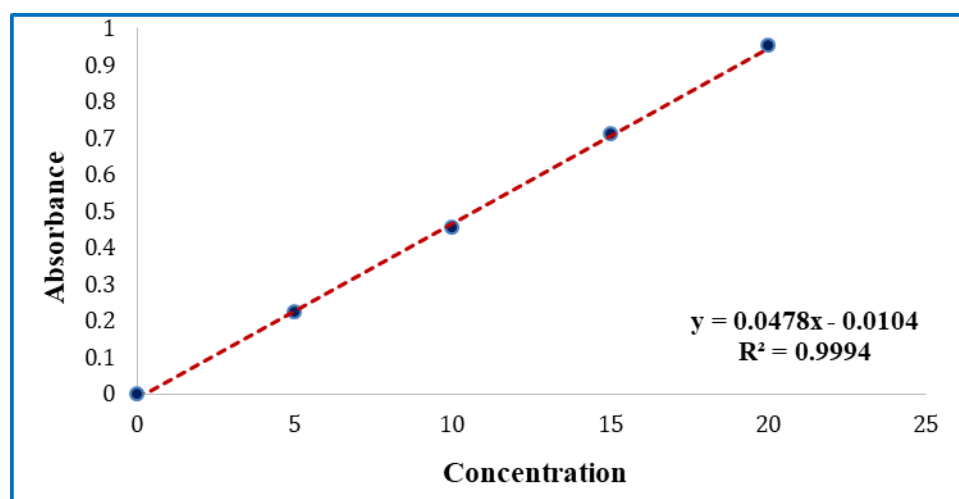


Figure 2: Standard calibration curve of Caffeine Anhydrous for pH 7.4 buffer.

2. Pre-filling parameters of granules

As mentioned in Table 5, the wet granulation process successfully minimized inter-particulate friction,

resulting in excellent flow properties, which are suitable for capsule filling.

Table 5: Pre-Filling Parameters Of Granules.

Formulation	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F1	0.60	0.65	7.69	1.08	22.44
F2	0.66	0.70	5.71	1.06	21.94
F3	0.65	0.72	9.72	1.10	22.28



Figure 3: Physical appearance of Caffeine Anhydrous granules and filled capsules.

Figure 3 shows the physical appearance of the prepared granules and filled hard gelatin capsules, demonstrating uniform granulation and successful encapsulation.

from 21.32 mm to 21.41 mm, falling within the literature reported limit of ~21.6 mm. All formulations passed the IP weight variation limits ($\pm 7.5\%$).

3. Post-filling Parameters of Capsules

a) Locking Length and Weight Variation

The filling and locking process maintained strict physical integrity. As shown in Table 6, locking lengths ranged

Table 6: Capsule Physical Parameters.

Formulation	Locking Length (mm)	Average Filled Wt. (mg)	% Range of Deviation
F1	21.41	500.9	+1.81%, -1.77%
F2	21.32	499.4	+2.12%, -1.68%
F3	21.35	501.5	+1.69%, -1.29%

b) Content Uniformity

The content uniformity of Caffeine Anhydrous remained within the limits, indicating highly effective drug-excipient blending. F1 yielded an average purity of 98.77%, F2 yielded 101.09%, and F3 yielded 99.83%.

c) In-Vitro Disintegration Test

All three formulations fulfilled the requirements for immediate-release profiles, demonstrating complete disintegration within 2 to 6 minutes (Table 7).

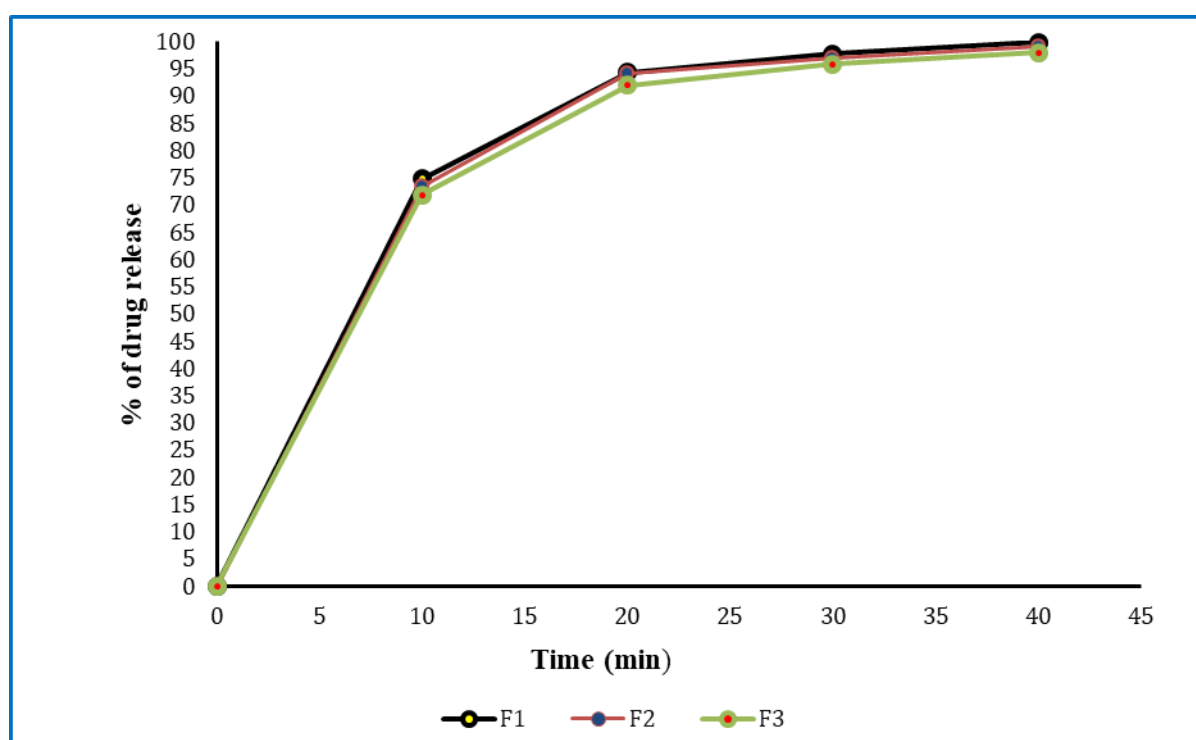
Table 7: Average Disintegration Time.

Formulation	Shell Rupture Time	Disintegration Time (Complete)
F1	1.44 min	2.46 min
F2	2.19 min	5.39min
F3	1.57 min	5.14 min

d) In-Vitro Dissolution Studies

The dissolution profiles demonstrated the influence of the selected filler matrices on drug release (Table 8). Formulation F1 (Mannitol) achieved the most rapid and complete drug release (99.81% at 40 min). Formulation

F2 (Lactose Monohydrate) exhibited a slightly slower but steady release profile (99.16% at 40 min) due to a less aggressive dissolution mechanism than mannitol. Formulation F3 (Dicalcium Phosphate) yielded the slowest release (97.97% at 40 min).

**Figure 4: In-vitro dissolution profile of Caffeine Anhydrous (F1-F3)****Table 8: Cumulative Drug Release Percentage in pH 1.2 Buffer.**

Time (min)	F1 (% Release)	F2 (% Release)	F3 (% Release)
10	74.79	73.41	71.90
20	94.35	94.06	91.93
30	97.74	97.09	95.90
40	99.81	99.16	97.97

e) Microbial Content Test

Following 48 hours of incubation at 37°C, F1 and the negative control exhibited no microbial colonies,

whereas the positive control exhibited visible colonies, confirming the microbiological safety of the optimized batch.

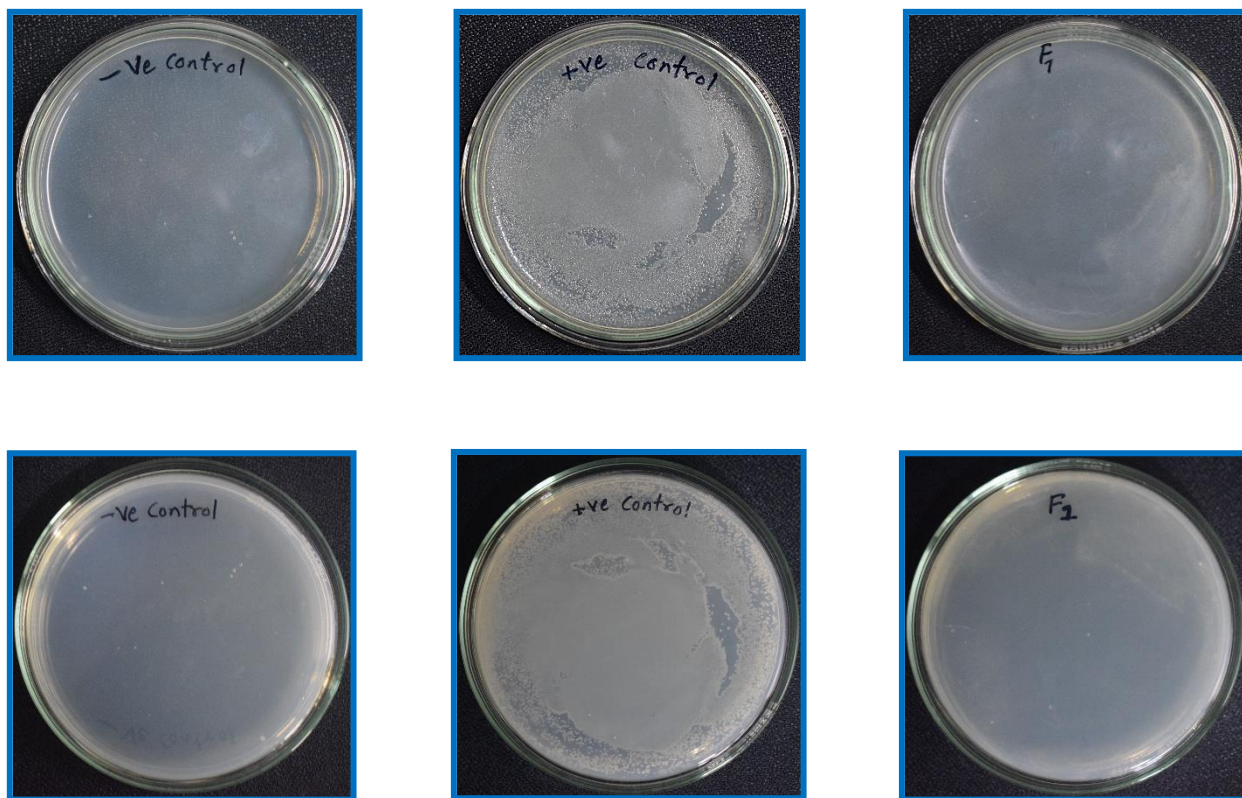


Figure 5: Microbial test culture plates of -ve control, +ve control and F1, showing top view (first row) and bottom view (second row) of the plates.

CONCLUSION

Immediate-release capsules of Caffeine Anhydrous (100 mg) were successfully developed using wet granulation method. In pre-filling parameters, micromeritics assessments confirmed excellent granular flowability across all three formulations. Filling and encapsulation operations maintained strict precision, ensuring all batches passed compendial limits for weight variation, content uniformity and literature reported limit of locking length. The excipient matrix selection significantly influenced the drug release profile. Formulation F1, formulated with Mannitol, outperformed Lactose Monohydrate and Dicalcium Phosphate matrices by providing the most rapid and complete dissolution profile. This faster dissolution of F1 may be due to higher water solubility of Mannitol and its ability to promote rapid liquid penetration into the granules. All formulations achieved rapid disintegration within 2 to 6 minutes, and microbial testing results indicates satisfactory microbiological quality of F1. Finally, based on evaluation parameters, F1 demonstrated the most favourable overall performance among all three formulations.

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