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FORMULATION AND EVALUATION OF MEDICATED CHEWING GUM

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ABSTRACT

Aim: Medicated Chewing Gum (MCG) is an innovative drug delivery method that utilizes chewing to dispense Gallic Acid, the key active component. This compound is employed for its localized effects or for absorption through the buccal mucosa. The main objective of MCG is to alleviate anxiety by enabling a regulated release of the active ingredient. **Method:** MCGs were formulated using conventional techniques with Gallic Acid serving as the active element. Two gum base polymers, Polyvinylpyrrolidone (PVP) and Eudragit L-100, were utilized to ensure the desired texture and chewiness. The products were evaluated based on pre-compression parameters (angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio) and post-compression parameters (weight variation, moisture content, elasticity, friability, drug content, *in-vitro* drug release, and antioxidant activity). The antioxidant potential was measured using the Ferric Reducing Antioxidant Power (FRAP) assay. **Results:** Four batches of formulations were prepared, with Batch 2 showing the best performance in both pre-compression and post-compression tests. The FRAP assay displayed antioxidant activity at various concentrations (20, 40, 60, 80, 100 µg/mL), yielding FRAP values of 0.4106, 3.4814, 4.2341, 4.2479, and 4.6686, respectively. The IC50 value for Gallic Acid was found to be 4.4475 µg/mL, while Ascorbic Acid, the reference drug, had an IC50 of 4.594 µg/mL. **Conclusion:** The optimized formulation of Medicated Chewing Gum containing Gallic Acid shows significant potential in providing

anxiety-reducing effects, backed by favourable physical attributes, effective drug release characteristics, and strong antioxidant activity.

KEYWORDS: Medicated chewing gum, Gallic acid, Anxiety, Antioxidant.

INTRODUCTION

Medicated Chewing Gum (MCG) represents a novel and mobile drug delivery system that facilitates the administration of active pharmaceutical ingredients in a convenient and patient-friendly format.[1] Unlike conventional dosage forms, MCG utilizes mastication to initiate drug release, enabling both localized therapeutic effects and systemic absorption via the buccal mucosa.[2] The buccal route offers distinct pharmacokinetic advantages, including rapid onset of action, avoidance of first-pass hepatic metabolism, and improved bioavailability due to its rich vascular network.[3] Gallic Acid, a naturally occurring phenolic compound, has garnered significant interest for its multifaceted pharmacological profile, encompassing antioxidant, anti-inflammatory, and anxiolytic properties.[4,5] Its incorporation into MCG offers dual therapeutic potential: localized action within the oral cavity and systemic efficacy through buccal absorption. Notably, the antioxidant capacity of Gallic Acid contributes to the mitigation of oxidative stress, a key factor implicated in anxiety and related neuropsychiatric conditions. In this study, Gallic Acid was incorporated into MCG formulations using gum base polymers such as Polyvinylpyrrolidone (PVP) and Eudragit L-100, selected for their favourable mechanical and masticatory characteristics. The resulting formulations were evaluated for physicochemical properties, in vitro drug release kinetics, and antioxidant activity, as assessed by the Ferric Reducing Antioxidant Power (FRAP) assay. This research aims to elucidate the potential of MCG as an innovative platform for anxiety management, emphasizing the therapeutic relevance and antioxidant efficacy of Gallic Acid. The results contribute to the growing body of research on buccal drug delivery systems and support the development of effective, non-invasive, and patient-centric pharmaceutical interventions.

MATERIALS AND METHODOLOGY

MATERIALS

All materials utilized in the formulation of Medicated Chewing Gum (MCG) were sourced from certified suppliers to ensure quality and consistency. The gum base polymers included Polyvinylpyrrolidone (PVP), procured from Balaji Drug, and Eudragit L-100, obtained from Chemdyes. Excipients such as dextrose, sucrose, and beeswax were supplied by Sulabh.

Calcium carbonate and ascorbic acid were procured from Qualikems, while polyethylene glycol (PEG-400), also sourced from Sulabh, was incorporated as a plasticizer to enhance the formulation's consistency.

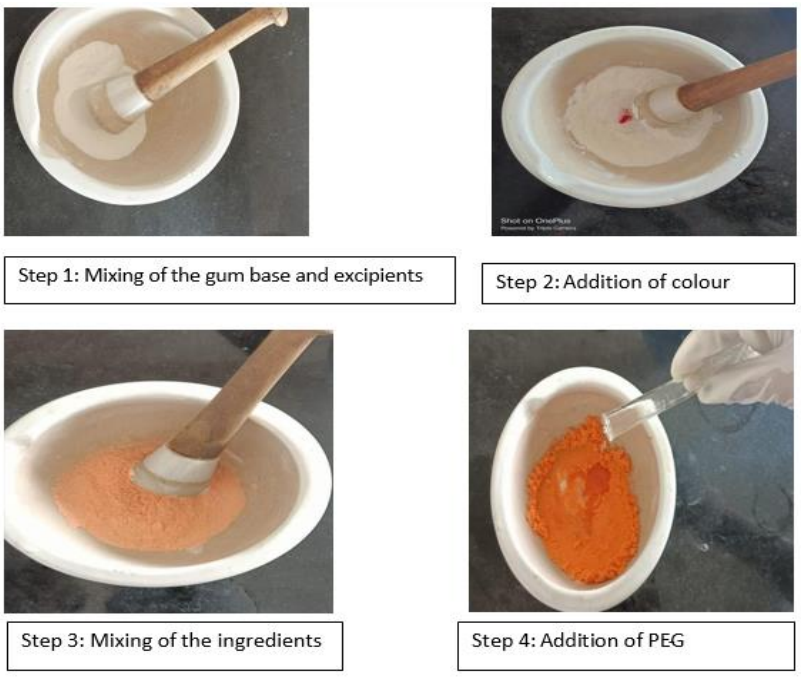
METHOD OF PREPARATION

Formulation of medicated chewing gum

MCG was prepared using the rolling technique. All ingredients—PVP, Eudragit L-100, beeswax, dextrose, sucrose, calcium carbonate, and ascorbic acid—were accurately weighed and sequentially combined in descending order of their respective weights. The components were homogenized using a mortar and pestle to achieve a uniform blend. Subsequently, a pre-measured quantity of PEG-400 was added to the mixture and thoroughly mixed until a cohesive and pliable mass was formed. The final blend was manually rolled to achieve the desired shape and thickness characteristic of chewing gum formulations.[6] (Table 1)

Preparation of anti-adherent layer

The anti-adherent layer was formulated via the trituration method to improve the handling and performance characteristics of the medicated chewing gum. Ingredients were accurately weighed and combined in descending order of their respective weights. The mixture was thoroughly triturated in a mortar to ensure homogeneity and optimal particle dispersion. The resulting blend was subsequently incorporated into the chewing gum matrix to minimize adhesion and facilitate ease of processing and administration.[7] (Figure 1)



Step 5: Prepare a damp mass

Step 6: Prepared Chewing gum

Figure 1: Pictorial Representation of Formulation.

Table 1: Formulation of Medicated Chewing Gum.

Srno	Ingredients	MCGG1	MCGG2	MCGG3	MCGG4
1	Polyvinyl pyrrolidone(gm)	4	4.5	5	5.5
2	Dextrose(gm)	1.5	3	4.5	6
3	Sucrose(gm)	6	4.5	3	1.5
4	Beeswax(gm)	1	1	1	1
5	Calcium carbonate(gm)	0.5	0.5	0.5	0.5
6	PEG-400(ml)	0.8	0.8	0.8	0.8
7	Orange oil(ml)	0.1	0.1	0.1	0.1
8	Eudragit(gm)	0.1	0.2	0.1	0.2
9	Colouring agent(gm)	q. s.	q. s.	q. s.	q. s.
10	Flavouring agent(ml)	q. s.	q. s.	q. s.	q. s.
11	Glycerine(ml)	0.1	0.2	0.1	0.2
12	Ascorbic acid(gm)	0.2	0.2	0.2	0.2
13	Gallic acid(mg)	97.2	97.2	97.2	97.2

EVALUATION OF MEDICATED CHEWING GUM

1. Organoleptic Analysis

The formulated Medicated Chewing Gum was subjected to organoleptic evaluation including appearance, texture, and aroma. These qualitative parameters are critical for patient acceptability and compliance.

2. Pre-Compression Studies

To evaluate the flowability and compressibility of the gum base and drug-excipient mixtures, standard pre-compression parameters like Angle of Repose, Bulk Density and Tapped Density, Compressibility Index (Carr's Index), Hausner's Ratio. These parameters collectively provide insight into the handling and processing behavior of the formulation prior to compression or shaping.[8,9]

3. Post-Compression Evaluation[10]

Moisture Content

Moisture content was determined using a desiccator containing a suitable desiccant, such as silica gel or anhydrous calcium chloride, to absorb residual moisture from the chewing gum samples. The moisture content was calculated using the following formula:

$$\text{Moisture Content (\%)} = \left(\frac{W_1 - W_2}{W_1}\right) \times 100$$

Where:

W_1 = Initial weight of the chewing gum

W_2 = Weight after drying in the desiccator

Drug Content Analysis

Drug content uniformity was evaluated by assaying five individual units of the MCG formulation for Gallic Acid concentration. Each unit was dissolved in 100 mL of artificial salivary fluid, followed by filtration and appropriate dilution. The absorbance of the resulting solution was measured using UV spectroscopy at 278 nm. Results were expressed as mean drug content ± standard deviation (SD). The formulation complies with pharmacopeial standards if the drug content of each unit falls within the range of 85% to 115% of the labelled amount. The composition of artificial salivary fluid in shown in Table 2.

Table 2: Composition of artificial salivary fluid.[11]

Sr. No.	Composition	(gm/l)
1.	Potassium dihydrogen 0-phosphate	0.34
2.	Di sodium hydrogen O-phosphate	0.43
3.	Potassium bicarbonate	1.50
4.	Sodium chloride	0.58
5.	Magnesium chloride	0.14
6.	Calcium chloride	0.22
7.	Citric acid	0.03
8.	pH adjusted to 6.7 with NaOH or HCL	

Friability Test

Friability was assessed by subjecting five chewing gum units to mechanical stress using a friabilator. The samples were placed on a rotating disc and subjected to 10 rotations. According to established criteria, the formulation passes the friability test if the percentage weight loss is less than 1%.[8]

Weight Variation

Twenty units of the Medicated Chewing Gum formulation (MCGG) were randomly selected and individually weighed. The average weight was calculated, and each unit's deviation from the mean was assessed. According to pharmacopeial standards, the maximum permissible deviation from the average weight should not exceed 5%.

***In-vitro* drug release**

The drug release profile of the Medicated Chewing Gum (MCG) formulation was evaluated using a magnetic stirrer-based in-vitro simulation of mastication. A glass beaker containing 50 mL of artificial salivary fluid (ASF) served as the test cell. The chewing gum sample was placed in the beaker, and the apparatus was operated at a simulated chewing frequency of 50 revolutions per minute (rpm).

Aliquots of 2 mL were withdrawn from the test cell at predetermined time intervals of 5, 10, 15, 20, 25, and 30 minutes. Following each withdrawal, an equal volume (2 mL) of fresh ASF was replenished to maintain sink conditions. The withdrawn samples were diluted to a final volume of 10 mL with ASF, and the absorbance was measured at 278 nm using UV-visible spectroscopy to quantify the release of Gallic Acid.[12]

***IN-VITRO* ANTIOXIDANT ACTIVITY**

FRAP Assay

The total antioxidant capacity of each sample was assessed using the Ferric Reducing Antioxidant Power (FRAP) assay, which evaluates the reducing ability of antioxidant compounds. In this assay, antioxidants reduce ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}), which subsequently form a blue-coloured complex with 2,4,6-tripyridyl-s-triazine (TPTZ). This complex (Fe^{2+}/TPTZ) exhibits a characteristic absorbance at 750 nm. (Figure 2) The FRAP reagent was freshly prepared by combining the following solutions in a 10:1:1 volume ratio:

- Acetate buffer (300 mM, pH 3.6)
- TPTZ solution (10 mM in 40 mM HCl)
- Ferric chloride solution (20 mM $FeCl_3$)

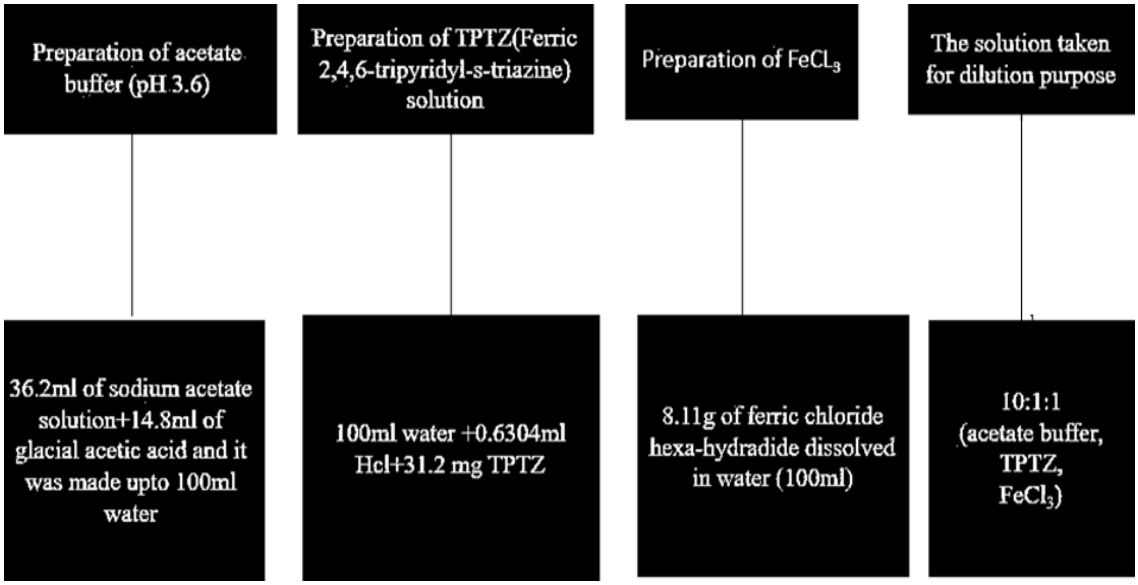


Figure 2: Preparation of solution used in FRAP Reagent.

For each measurement, 3 ml of the FRAP reagent was mixed with varying volumes (0.2, 0.4, 0.6, 0.8, and 1.0 ml) of the sample solution. The final volume was adjusted to 10 ml using distilled water. After 30 minutes of incubation, the development of a dark blue color indicated the formation of the Fe^{2+}/TPTZ complex. Absorbance was then recorded at 750 nm.

The FRAP value was calculated directly from the absorbance readings. All measurements were performed in triplicate for each extract to ensure reproducibility and accuracy.[13,14]

The antioxidant activity was quantified using the following formula:

$$\text{FRAP Value} = \frac{A_1 - A_0}{A_c - A_0} \times 2$$

Where

- A_1= Absorbance of the sample
- A_0= Absorbance of the blank
- A_c= Absorbance of the ascorbic acid standard

This calculation enables comparison of the sample's antioxidant potential relative to a known standard.[15]

RESULTS

1) **Pre-compression study: Flow properties of the gum base and drug excipient mixtureswere evaluated.**

Table 3: Pre-compression study of gum base and excipients.

Sr.no.	Flow properties	Components	Average values
1	Bulk density(gm/ml)	Gum base Excipients	0.56±0.12 0.52±0.06
2	Tapped density(gm/ml)	Gum base Excipients	0.65±0.14 0.61±0.17
3	Hausner's ratio	Gum base Excipients	1.16±0.05 1.17±0.03
4	Compressibility index (%)	Gum base Excipients	13%±0.62 14.75%±0.18
5	Angle of repose(θ)	Gum base Excipients	22.16±1.20 29.28±1.78

2) **Post-compression study:** To obtain good chewability, flavoring, sweetness, softening, and elasticity of the chewing gum, different batches of MCGGs were formulated.

Table 4: Post-compression study of medicated chewing gum.

Properties	MCGG1	MCGG2	MCGG3	MCGG4
Softener	Very hard	Soft	Passable	Passable
Elasticity	Good	Very Good	Good	Good

Moisture content: The mean moisture content for each formulation was determined and summarized in Table 5.

Table 5: Moisture Content of formulations.

Properties	MCGG1	MCGG2	MCGG3	MCGG4
Initial Weight	0.76	0.79	0.77	0.77
Final Weight	0.74	0.78	0.76	0.75
Moisture Content (%)	2.63	1.26	1.30	2.60

Drug Content: The formulation complies with the drug content test, showing 95.88%, which falls within 85–115% of the average content.

Friability: As per the literature if the percentage of friability is less than one then the formulation passes the test. The percentage friability of the chewing gum was found to be 0.07% within the range. Hence, the formulation passes the test.

Weight variation: The variation in the weight of the prepared chewing gum is reported in Table 6.

Table 6: Weight Variation of medicated chewing gum.

Sr no.	Each Chewing gum weight (gm)	% deviation
1	0.73	-0.043
2	0.75	-0.023
3	0.74	-0.033
4	0.81	+0.037
5	0.79	+0.017
6	0.77	-0.003
7	0.77	-0.003
8	0.79	+0.017
9	0.80	+0.027
10	0.81	+0.037
11	0.76	-0.013
12	0.74	-0.033
13	0.75	-0.023
14	0.78	+0.007
15	0.80	+0.027
16	0.82	+0.047
17	0.76	-0.013
18	0.76	-0.013
19	0.75	-0.023
20	0.78	+0.007

Percentage Cumulative Drug Release: The percentage cumulative drug release (CDR) was calculated for each batch based on absorbance values. At 30 minutes, the CDR was 69.80% for MCGG1, 74.17% for MCGG2, 28.34% for MCGG3, and 35.46% for MCGG4. (Table 7)

Table 7: Percentage Cumulative Drug Release of MCG formulations.

Time (minutes)	MCGG1	MCGG2	MCGG3	MCGG4
5	10.33	11.22	3.56	4.60
10	21.14	22.71	7.41	9.72
15	32.60	34.83	11.77	15.45
20	44.50	47.36	16.74	21.62
25	56.86	60.38	22.36	28.23
30	69.80	74.17	28.34	35.46

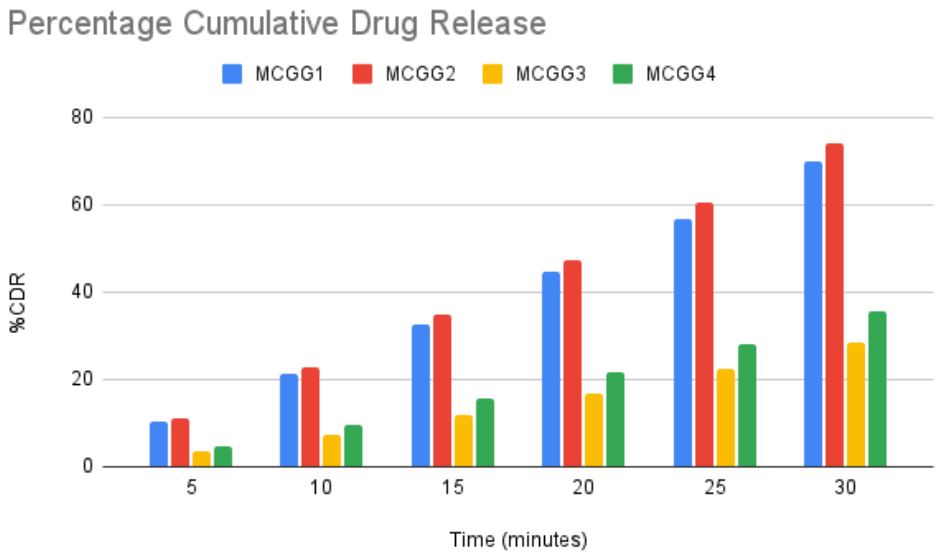


Figure 3: Percentage Cumulative Drug Release.

Invitro Antioxidant assay

For the evaluation of the FRAP assay, the FRAP value was directly calculated from the absorbance. Frap values are significant in evaluating the antioxidant capacity. These values indicate the ability of a substance to reduce ferric ions to ferrous ions in an acidic medium and higher frap values suggest greater antioxidant activity which is important for protecting cells from oxidative stress and related damage. Figure 3 shows the calculated FRAP values at different concentrations (20 to 100 µg/ml). The increased antioxidant activity was observed with the increased FRAP values. (Figure 4).

FRAP assay

The reducing power (absorbance) of gallic acid and ascorbic acid was determined at different concentrations (20, 40, 60, 80, and 100 µg/ml). As shown in Table 8, the reducing power of both compounds increased with concentration. For gallic acid, absorbance values ranged from 0.1385 at 20 µg/ml to 1.0751 at 100 µg/ml. For ascorbic acid, absorbance values ranged from 0.2132 at 20 µg/ml to 0.5287 at 100 µg/ml (Figure 5). The IC_{50} was calculated from the absorbance graph at 750 nm.

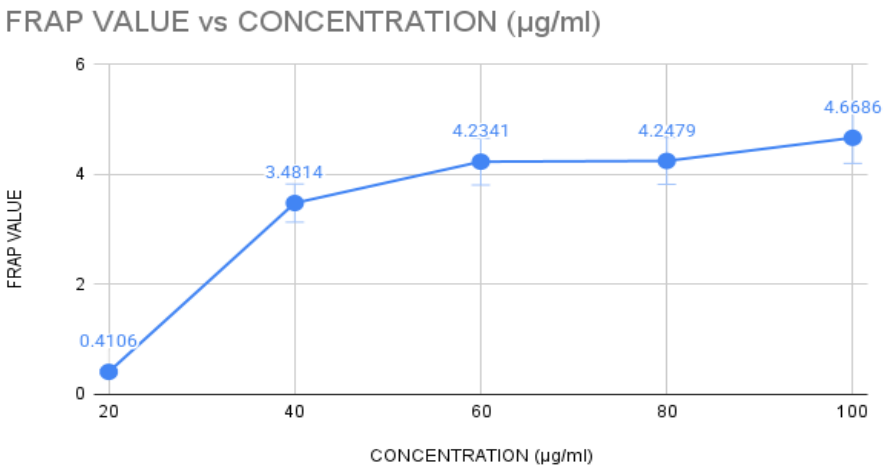


Figure 4: Plot of FRAP value V/S concentration.

IC50 Value indicates how much of a drug is needed to inhibit a biological process by half.

The formula to calculate the IC50 value

$$IC50=0.5-a/b$$

Where a=slope and b= intercept

Table 5: FRAP Assay of Gallic acid and Ascorbic acid.

Concentration (µg/ml)	Gallic Acid		Ascorbic Acid	
	Absorbance (750nm)	IC50 0.5 –a/b	Absorbance (750nm)	IC50 0.5-a/b
20	0.1385	4.4475	0.2132	4.594
40	0.3542		0.2542	
60	0.6165		0.3541	
80	0.9089		0.491	
100	1.0751		0.5287	

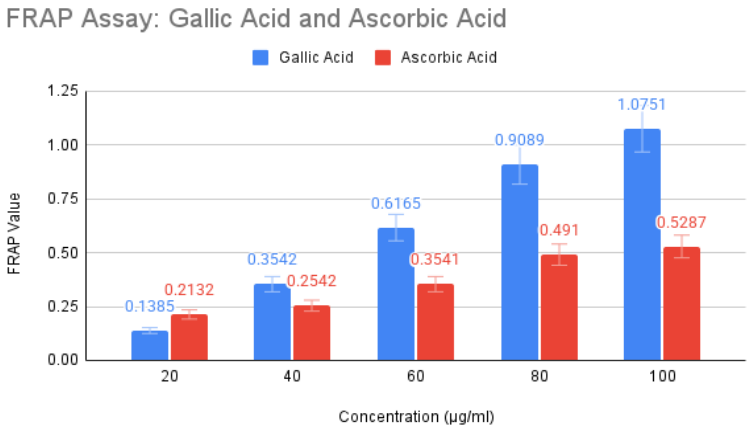


Figure 5: Plot of FRAP Assay of ascorbic acid (standard) and gallic acid.

DISCUSSION

The evaluation of the Medicated Chewing Gum (MCG) formulation revealed promising results across both pre-compression and post-compression parameters, indicating its suitability for therapeutic use. The pre-compression studies demonstrated favorable physical properties for both the gum base and excipients. Bulk and tapped density values fell within acceptable ranges, suggesting good packing characteristics. The angle of repose values—22.16°±1.20 for the gum base and 29.28°±2.12 for the excipients—indicated adequate flowability, further supported by Hausner's ratios of 1.16 ±0.011 and 1.17±0.011, respectively, which are consistent with optimal flow behavior. The compressibility index values (13%±0.62 for gum base and 14.75% ±0.18 for excipients) also confirmed the materials suitability for compression, aligning with standard pharmaceutical benchmarks. The weight variation test confirmed uniformity, with 90% of the tested units falling within the permissible deviation, ensuring dose consistency. *In vitro* drug release studies demonstrated a positive correlation between chewing time and drug release, with Batch MCGG2 showing the highest release profile. This suggests that the mechanical action of chewing effectively facilitates drug dispersion, a key consideration in gum-based drug delivery. Drug content analysis further validated the formulation's reliability, with all samples falling within the acceptable range of 85%–115% of the average content. Friability and moisture content assessments indicated good mechanical stability and shelf-life potential, with a low moisture content of 2.63%, 1.26%, 1.30%, 2.60% for MCGG1, MCGG2, MCGG3, MCGG4 respectively. The low moisture content supports long-term preservation. The antioxidant potential of Gallic Acid, evaluated via the Ferric Reducing Antioxidant Power (FRAP) assay, showed a concentration-dependent increase in activity. This was evidenced by progressively higher FRAP values across increasing concentrations, confirming its efficacy. The IC_{50} values for Gallic Acid (4.4475 µg/mL) and Ascorbic Acid (4.594 µg/mL) further substantiated the potent antioxidant properties of Gallic Acid, suggesting its potential role in enhancing the therapeutic value of the formulation. Overall, the comprehensive evaluation supports the viability of MCG as a novel drug delivery system, with Batch MCGG2 emerging as the optimal formulation. The incorporation of Gallic Acid adds functional value through its antioxidant properties, potentially contributing to broader health benefits.

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