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Microencapsulation of Ranitidine Hydrochloride for Controlled Release Drug Formulation

Darshil Vaylu[1], Bhargavi Chaudhary[1], Ark Patel[1], Aditya Singh*[2], Shubhrat Maheshwari[3]

[1]Institute of Pharmacy, Nirma University, Sarkhej–Gandhinagar Highway, Ahmedabad – 382481, Gujarat, India
[2]Department of Pharmaceutics, Parul Institute of Pharmacy & Research, Parul University, Waghodia, Vadodara, Gujarat 391760, India
[3]Bioorganic and Medicinal Chemistry Research Laboratory, Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Prayagraj, 211007, India.

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Corresponding Author:
simmu5adityasingh@gmail.com

Abstract

The present study explored the microencapsulation of ranitidine hydrochloride to develop a controlled-release formulation aimed at improving bioavailability, reducing dosing frequency, and enhancing drug stability. Ranitidine, a H_2-receptor antagonist, is commonly used in the treatment of gastrointestinal disorders such as acid reflux, peptic ulcers, and Zollinger–Ellison syndrome. However, its conventional formulations are limited by a short half-life, poor stability, and the potential formation of N-nitrosodimethylamine (NDMA), a probable human carcinogen. To overcome these limitations, microencapsulation was employed using polymers such as Hydroxypropyl Methylcellulose (HPMC) and Microcrystalline Cellulose (MCC 102). The drug–polymer mixture was prepared using the extrusion–spheronization technique, followed by spray drying and pelletization. Various formulations were optimized by altering the drug-to-polymer ratio and solvent system (isopropyl alcohol and water). The prepared microcapsules and pellets were evaluated for physicochemical properties, including particle size, morphology, encapsulation efficiency, zeta potential, and surface characteristics using UV–Visible spectrophotometry, dynamic light scattering (DLS), and scanning electron microscopy (SEM). In vitro dissolution studies demonstrated a sustained drug release profile, which followed zero-order and Higuchi kinetic models, indicating controlled drug release behavior. The microencapsulation approach effectively minimized the degradation of ranitidine and ensured a more consistent release under simulated gastric conditions. Compatibility and stability studies further confirmed that HPMC and MCC-based formulations provided enhanced protection against hydrolysis and environmental stress. Overall, the findings suggest that microencapsulation is a promising strategy for reformulating ranitidine, offering improved therapeutic efficacy, controlled drug release, and better patient compliance. This study also provides a foundation for extending microencapsulation approaches to other drugs with short half-lives or stability concerns.

INTRODUCTION

Microencapsulation is defined as the process of enclosing small particles or droplets within a coating material to form capsules. This technique produces microcapsules that exhibit beneficial properties such as controlled drug release, enhanced stability, and protection against environmental factors such as light, moisture, and oxygen [1]. Microencapsulation is widely applied in pharmaceuticals, food technology, and agriculture for encapsulating active ingredients such as drugs, flavors, and pesticides. The primary objective of microencapsulation is to improve the functionality and effectiveness of active substances by enabling controlled and sustained release, protecting the core material from external degradation, facilitating targeted delivery, and extending the shelf life of sensitive compounds.

Ranitidine is a histamine H_2-receptor antagonist that reduces gastric acid secretion. It has been widely used in the treatment of gastrointestinal disorders such as gastroesophageal reflux disease, peptic ulcers, and Zollinger–Ellison syndrome. However, due to the detection of N-nitrosodimethylamine (NDMA), a probable human carcinogen, ranitidine has been withdrawn from several markets worldwide [2].

The present study focuses on the development of floating microspheres of ranitidine hydrochloride using polymers such as ethyl cellulose and Eudragit E100, prepared by the emulsion solvent evaporation method. The prepared microspheres were evaluated for buoyancy, drug release, entrapment efficiency, and production yield. The optimized formulation exhibited sustained drug release over 12 hours, high buoyancy (up to 92%), and good flow properties [3].

Pre-formulation testing involves the investigation of the physicochemical properties of a drug substance, both alone and in combination with excipients. It represents the initial stage in the rational development of dosage forms. The main objective of pre-formulation studies is to provide essential data to formulate stable, bioavailable, and manufacturable dosage forms. These studies help in identifying the physical and chemical characteristics of both drug and excipients that may influence formulation design, manufacturing processes, pharmacokinetics, and biopharmaceutical performance of the final product [4].

The melting point is defined as the temperature at which a solid substance changes into a liquid. This parameter was determined using a melting point apparatus. A small quantity of the drug was filled into a capillary tube and placed in the apparatus. The temperature at which the drug melted was recorded using a calibrated thermometer [5].

A calibration curve represents the relationship between the measured absorbance and known concentrations of a substance. A stock solution was prepared by dissolving 10 mg of salicylic acid in 100 mL of solvent to obtain a concentration of 100 µg/mL. Further dilutions were made to obtain concentrations of 20, 40, 60, and 80 µg/mL by transferring appropriate volumes (2, 4, 6, and 8 mL) into 10 mL volumetric flasks and making up the volume with solvent. The absorbance of these solutions was measured at 300 nm using a UV spectrophotometer, and a calibration curve was plotted [6].

Drug–excipient compatibility studies were carried out using Fourier Transform Infrared (FTIR) spectroscopy. The FTIR spectra of the pure drug, excipients, and the final formulation were compared to identify any possible interactions. Characteristic functional group peaks were analyzed, and any shift, disappearance, or appearance of new peaks indicated potential interactions between the drug and excipients [7].

MATERIALS AND METHOD

Ranitidine hydrochloride was obtained as a gift sample from a reputed pharmaceutical industry. Microcrystalline cellulose (MCC 102) and hydroxypropyl methylcellulose (HPMC K15) were procured from reliable commercial suppliers. Distilled water was prepared in the laboratory and used throughout the study. Analytical grade solvents, including isopropyl alcohol (IPA), 0.1 N hydrochloric acid, and buffer

solutions, were used as received. Potassium chloride (KCl) of analytical grade was also procured from standard chemical suppliers. All chemicals and reagents used in the study were of analytical grade and used without further purification.

Method of preparation

Ranitidine hydrochloride was dissolved in a suitable solvent system. Separately, the polymer solution was prepared by dissolving hydroxypropyl methylcellulose (HPMC K15) and microcrystalline cellulose (MCC 102) in the same or a compatible solvent. Both solutions were mixed thoroughly under continuous stirring to obtain a homogeneous feed solution. The prepared feed solution was then pumped into a spray dryer and atomized into fine droplets using a nozzle or rotary atomizer [8]. The droplets were dried in a stream of hot air under controlled conditions (inlet temperature: 120–200°C; outlet temperature: 50–90°C) to prevent thermal degradation of the drug. The resulting dried microparticles were collected using a cyclone separator and stored in an airtight container for further processing. The spray-dried microparticles were then blended with accurately weighed quantities of MCC 102 and HPMC K15 using a mortar and pestle for 10–15 minutes to ensure uniform mixing. A binding solution consisting of 5% isopropyl alcohol (IPA) in water was prepared and added gradually to the powder blend with continuous mixing until a cohesive, non-sticky wet mass with suitable plasticity was obtained. The wet mass was transferred to an extruder and processed at optimized speed to produce uniform cylindrical extrudates. The extrudates were immediately transferred to a spheronizer equipped with a cross-hatched friction plate. Spheronization was carried out at a rotor speed of 800–1200 rpm for 2–10 minutes to obtain spherical pellets. Finally, the pellets were dried in a hot air oven at 40–50°C until the moisture content was reduced to below 2%. Alternatively, a fluidized bed dryer may be used. The dried pellets were stored in airtight containers for further evaluation [9].

Optimization of batches

Thus, the polymer-to-drug ratio, feed viscosity, and drying parameters were optimized to achieve the desired particle size, encapsulation efficiency, and drug release profile (Tables 1–5) [10].

Table 1: Primary Batch 1 without API

Polymer		Amt. of solvent		Observation
MCC102(gm)	HPMCE15(gm)	IPA (mL)	Water (mL)	
7.5	7.5	10	10	Uniform in size and shape, Spherical, no signs of agglomeration
7.5	7.5	12.5	7.5	Uniform in size and shape, Spherical, no signs of agglomeration
7.5	7.5	15	5	Uniform in size and shape, Spherical, no signs of agglomeration

Table 2: Primary Batch 3 without API

Polymer		Amt. of solvent		Observation
MCC102(gm)	**HPMCE15(gm)**	**IPA (mL)**	**WATER (mL)**	
10	5	10	10	Roughly spherical to irregular in shape
10	5	12.5	7.5	Irregular in shape
10	5	15	5	Irregular shape and size

Table 3: Primary Batch 3 without API

Polymer		Amt. of solvent		Observation
MCC102(gm)	**HPMCE15(gm)**	**IPA (mL)**	**Water (mL)**	
12.5	2.5	10	10	Spherical but not uniform in size, slightly aggregation
12.5	2.5	12.5	7.5	Spherical but not uniform in size, slightly aggregation
12.5	2.5	15	5	Spherical but not uniform in size, slightly aggregation

Table 4: Primary Batch 4 with API

API(%/gm)	Polymer		Amt. of solvent		Observation
	MCC102(gm)	**HPMCE 15(gm)**	**IPA (mL)**	**Water(mL)**	
20%/4	8	8	10	10	Mostly spherical or near spherical, slightly variation in size
40%/15	11.25	11.25	15	15	Uniform granules, spherical, consistently sized, no agglomeration

Table 5: Primary Batch 5 with API

Polymer		Amt. of solvent		Observation
MCC102(gm)	HPMCE15(gm)	IPA (mL)	WATER (mL)	
12	3	10	10	Mostly spherical and uniform in size, Mild aggregation
12	3	12.5	7.5	Spherical, uniform
12	3	15	5	Uniform and Mild aggregation

Organoleptic Properties

The sample was observed under normal lighting, and its colour and physical appearance were noted [11].

Melting Point

A capillary tube was taken and filled with a small amount of the drug. It was then placed in the melting point apparatus. The temperature was increased gradually, and the melting temperature range was recorded [12].

UV-Visible Spectrophotometric Analysis of Ranitidine Hydrochloride

The standard stock solution was prepared by accurately weighing 100 mg of Ranitidine Hydrochloride and dissolving it in 0.1 N HCl, and the volume was made up to 100 mL (concentration = 1000 µg/mL). From this, 10 mL was diluted to 100 mL to obtain a 100 µg/mL stock solution. A series of dilutions was then prepared from the stock solution to obtain concentrations of 1, 2, 3, 4, 5, and 6 µg/mL [13].

A 10 µg/mL solution was taken and scanned in a UV spectrophotometer over the range of 200 to 400 nm. The λmax (typically around 313–315 nm in 0.1 N HCl) was determined. The absorbance of all working standard solutions was measured at λmax. A calibration curve was plotted with absorbance on the y-axis and concentration on the x-axis, and linear regression was performed to obtain the equation.

$A = \varepsilon bc$,

where:

A = absorbance

ε = molar absorptivity

b= path length (1 cm)

c = concentration in g/L

Characterization of Microencapsulated formulation

Encapsulation Efficiency

The percentage of entrapped drug/polymer in the total amount of drug introduced into the formulation was determined. The amount of ranitidine in the microcapsules was estimated by dissolving a known mass of the encapsulated product in a suitable solvent and measuring the absorbance at an appropriate wavelength (e.g., 314 nm). A more accurate method involved determining the amount of free drug present in the

supernatant after washing the microcapsules. The amount of drug encapsulated was then calculated by subtracting the free drug from the total drug content [14].

Release Profile of Drug

In-vitro release studies of ranitidine from the microcapsules were carried out under simulated conditions using the USP dissolution apparatus to mimic gastric and intestinal fluids (pH 1.2 and 6.8, respectively). Samples were withdrawn at predetermined time intervals and analyzed for drug content. The release data were fitted to various kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine the mechanism of drug release (diffusion, erosion, or both). A release profile curve was plotted as percentage drug release versus time [15].

Dissolution Test

A buffer solution was prepared by suspending 14.91 g of KCl in approximately 800 mL of distilled water. Separately, 0.2 M HCl was prepared by diluting 16.7 mL of concentrated HCl (37%) to 1 L with distilled water. The HCl solution was added gradually to the KCl solution with continuous stirring. The pH was monitored using a calibrated pH meter and adjusted to 2.0 by adding HCl dropwise. The solution was then transferred to a 1 L volumetric flask and the volume was made up with distilled water. The prepared solution was shaken, properly labeled, and stored in a tightly closed glass or HDPE container, and used within one week.

Disintegration Test

A sample weighing 100–200 mg of pellets was taken and placed in a disintegration test apparatus using a standard mesh. Water maintained at 37 ± 0.5°C was used as the medium. The time required for complete disintegration or dispersion of the pellets was recorded.

Drug Content

An accurately weighed 500 mg sample of the formulation was taken and triturated using a mortar and pestle to obtain fine particles. The powdered sample was transferred to a 100 mL beaker, and approximately 50 mL of distilled water was added. A magnetic stir bar was placed in the beaker, and the mixture was stirred for 30 minutes to ensure complete dissolution of the drug. The solution was then filtered to remove insoluble excipients and coating materials.

Standard Preparation

A standard solution of Ranitidine HCl (100 µg/mL) was prepared in distilled water. From this stock solution, working standards in the concentration range of 1–10 µg/mL were prepared. The absorbance of these solutions was measured at λmax (313–314 nm), where Ranitidine HCl exhibited maximum absorbance in water [16].

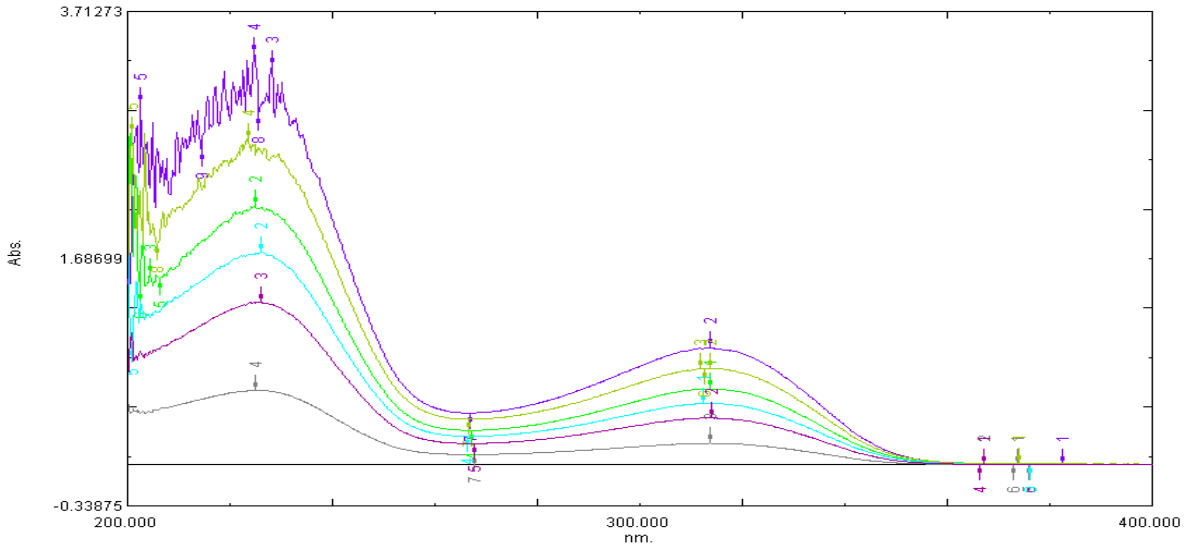
Result & Discussion

Pre-formulation Testing

The drug was found to be white to pale yellow in colour with a crystalline powder appearance. It was observed to be odourless. The drug was highly soluble in water and slightly soluble in alcohol. The melting point of Ranitidine hydrochloride was determined to be in the range of 133–134°C.

UV-Visible Spectrophotometric Analysis of Ranitidine Hydrochloride

Excellent linearity with the equations $Y = 0.1505x + 0.0437$ and $R^2 = 0.9936$ was demonstrated by the UV spectrophotometric analysis of ranitidine HCl, confirming compliance with Beer-Lambert's law. This confirms the accuracy and dependability of the method for quantitative analysis by showing a strong correlation between concentration and absorbance within the tested range. There appears to be little background interference based on the low intercept. These results lend credence to the preformulation study of ranitidine HCl using this UV method for routine analysis and formulation development (figure 1). All things considered, the approach is accurate, sensitive, and appropriate for drug estimation.



[A]

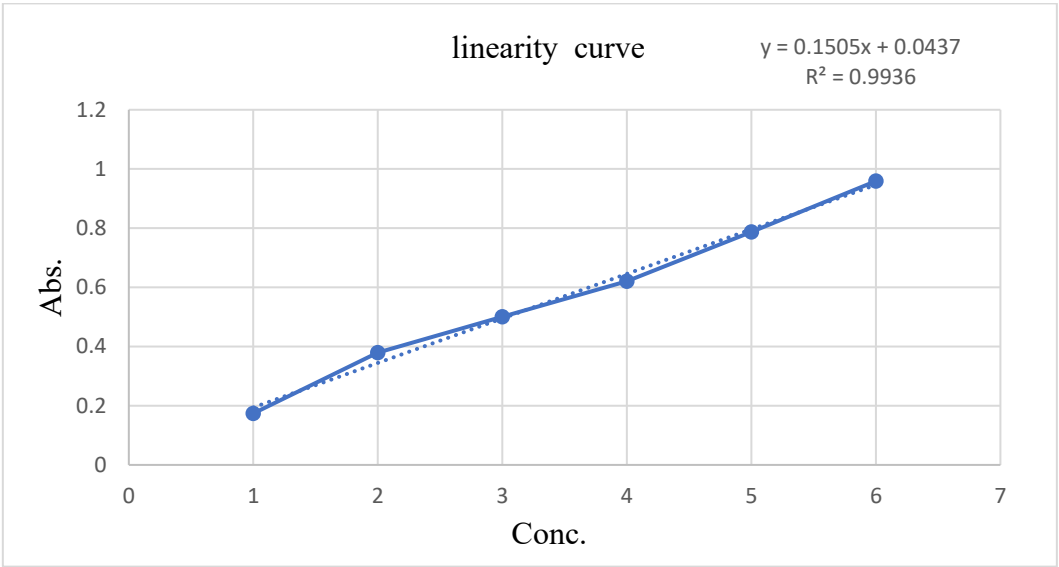


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Figure 1: Linearity curve of Ranitidine Hydrochloride

Dissolution Test

Standard calibration processing showed a strong positive correlation between absorbance and concentration at $R^2 = 0.9936$ using the equation $y = 0.1505x + 0.0437$. During the first 15 minutes a rapid drug release amounted to 0.44% was detected thus showing a limited burst release effect. The drug delivered a progressive and extended drug transport pattern after its initial fast release. During 240 minutes (4 hours) of assessment the drug delivery reached 28.84% of its total content. The effective controlled drug release pattern occurred when the cumulative drug release reached 51.76% at 480 minutes (8 hours). The microencapsulation method succeeded in managing drug delivery by regulating the drug releasing speed to provide extended-time sustained drug delivery. The controlled drug release pattern assists in keeping Ranitidine plasma levels stable which assists both the treatment outcomes and compliance from patients. Data shows that the drug release follows zero-order kinetics based on the steady linear connection between time and cumulative drug

amount released. Having this release method enables a steady total drug amount in circulating blood. The minimal drug release amount observed during the initial phase strengthens the microcapsule stability during acidic environments by reducing the degradation process and minimizing NDMA formation. Experimental dissolution results demonstrate that microencapsulation enables controlled drug release at a sustainable rate which confirms its capability for business and medical therapy usage. During a 480-minute period Sample 3 released drugs through a steady method at 40% drug concentration. After a period of 480 minutes the research demonstrated that the drug release began with 2.499 mg (1.666% CPR) at 15 minutes and reached 125.493 mg (83.662% CPR). Drug delivery through the diffusion-mechanism produces a controlled drug-release pattern resulting from multiple consecutive drug-release events. Over the 240 minutes stretch the drug release rate followed conventional sustained-release trends since the rate decreased along with the drug concentration decrease. The investigation produces consistent data because the measurement error remains constant throughout. The visual representations in extended-release data match the numerical values shown in both tables and graphs. The controlled release characteristics allow medical practitioners to give smaller dose quantities which improves both drug effectiveness and patient medication adherence during extended treatment periods. Sample 3 demonstrates drug release control that makes it an effective choice for pharmaceutical sustained release applications (figure 2 to figure 7) [17].

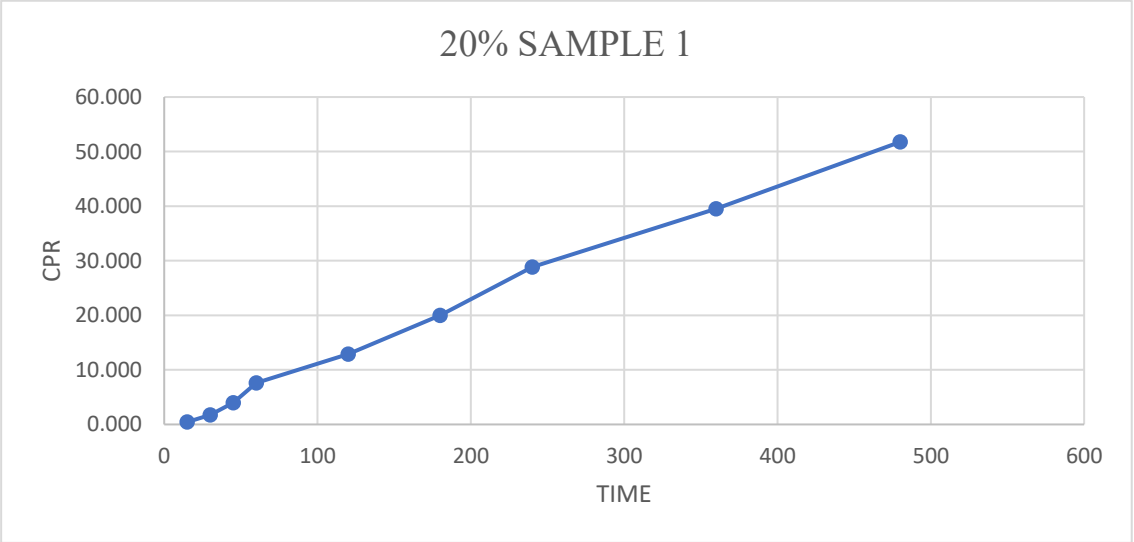

Figure 2: Dissolution sample 1(20%)

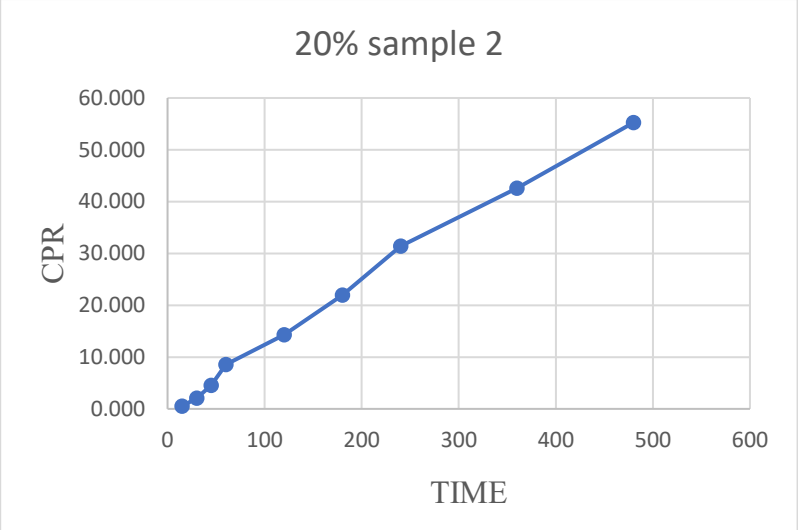

Figure 3: Dissolution Sample 2(20%)

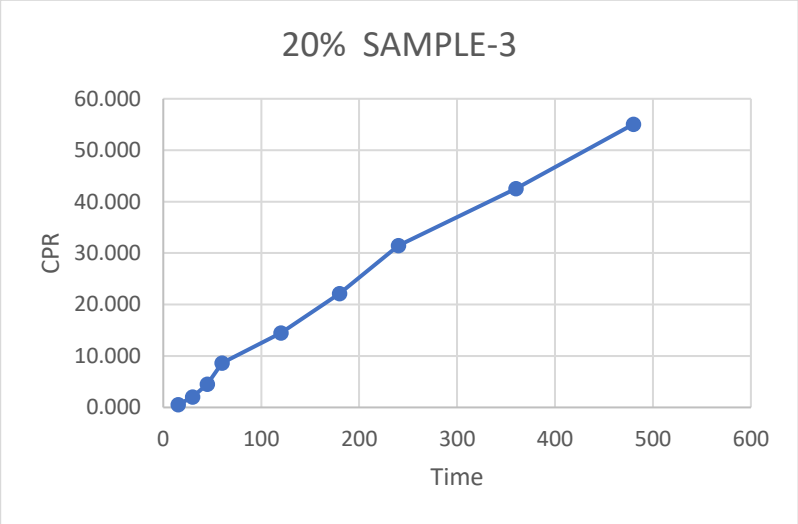

Figure 4: Dissolution Sample 3(20%)

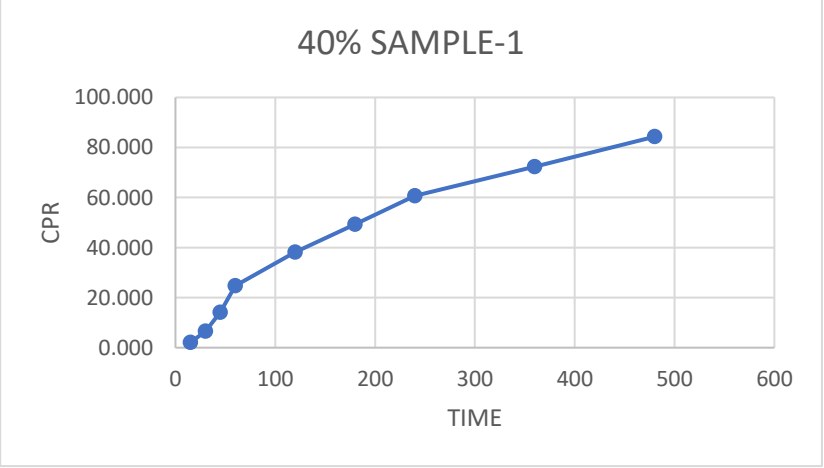

Figure 5: Dissolution Sample 1(40%)

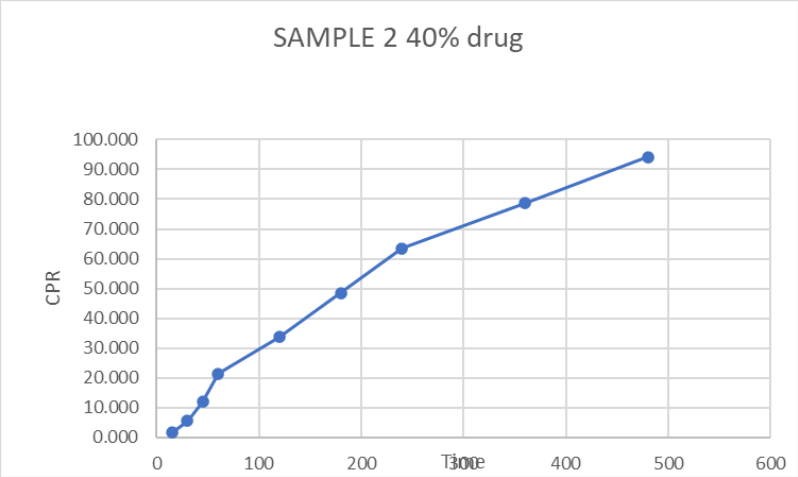

Figure 6: Dissolution Sample 2 (40%)

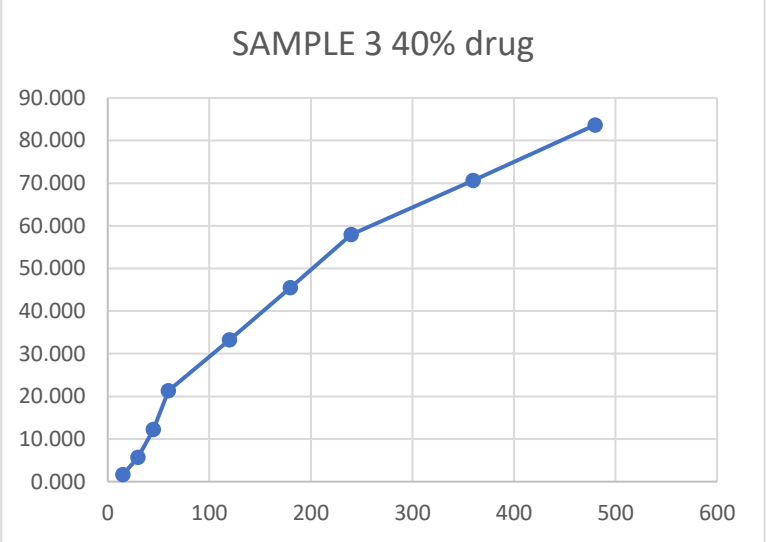

Figure 7: Dissolution sample 3 (40%)

Disintegration test

The potential for sustained drug release is demonstrated by the 2-hour disintegration time of the microencapsulated controlled-release formulation of ranitidine HCl. Long-term therapeutic action is supported by this prolonged disintegration, which lowers dosage frequency and increases patient compliance. The 2-hour breakdown time implies that the medication is released gradually while keeping plasma levels steady. Kinetic modelling, stability testing, and thorough release profiling should be the main topics of future research. Further validating the formulation's performance and clinical relevance as a controlled-release dosage form will involve conducting in vitro–in vivo correlation (IVIVC) studies and evaluating it under different pH conditions. The drug content of individual pellet samples remained within the pharmacopeial limits which extended between 85% to 115% when compared to the stated claim amount and it is shown in the table (table 6 & table 7). The therapeutic component spread evenly throughout

the pellets according to specifications. The stable distribution of test results between units confirms the correct combination process, acceptable palletization techniques and precise filling techniques for capsules or sachets. Dose accuracy relies heavily on this uniformity because sustained-release formulations need drug release to extend throughout the entire period [18].

Table 6: Drug content (20%)

Sr no	Abs.	DF	Conc.(mcq/ml)	Conc.*DF	Drug(mg)	Drug in 50ml
1	0.2469	1000	1.931229236	1931.22923	1.93122923	96.5614617
2	0.2454	1000	1.921328904	1921.32890	1.92132890	96.0664451
3	0.2565	1000	1.995016611	1995.01661	1.99501661	99.7508305

Table 7: Drug Content (40%)

Sr no	Abs.	DF	Conc. (mcq/ml)	Conc.*DF	Drug(mg)	Drug in 50ml
1	0.5526	1000	3.962657807	3962.65780	3.96265780	198.132890
2	0.5202	1000	3.746843854	3746.84385	3.74684385	187.342192
3	0.5345	1000	3.841993355	3841.99335	3.84199335	192.099667

CONCLUSION

The drug content of individual pellet samples was found to be within the pharmacopeial limits of 85% to 115% of the stated claim, as presented in Tables 4.5.1 and 4.5.2. This indicates that the formulation process achieved acceptable content uniformity, ensuring that each unit contained an appropriate amount of the therapeutic agent. The uniform distribution of the drug throughout the pellets suggests efficient mixing and proper incorporation of the drug during the formulation process.

The consistency observed among the pellet samples reflects the reliability of the pelletization technique employed, as well as the effectiveness of the blending and processing conditions. Additionally, the minimal variation in drug content confirms the adequacy of the encapsulation or filling process, whether in capsules or sachets, thereby ensuring reproducibility and batch-to-batch consistency.

Such uniformity is particularly critical in sustained-release formulations, where the controlled and prolonged release of the drug depends on consistent drug loading within each pellet. Any significant variation could lead to dose dumping or sub-therapeutic effects. Therefore, the observed results demonstrate that the formulation meets quality standards and is suitable for achieving the desired therapeutic performance over an extended period [19-20].

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Informed Consent

Not Applicable.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest among themselves. The authors alone are responsible for the content and writing of this article.

Financial Interests

The authors declare they have no financial interests.

Human and Animal Rights

NA

Ethics approval and consent to participate

Not applicable.

Authors Contributions

DV has written the manuscript, BC made the paper according to journal instruction and AS has prepared table and SM figure, and AP has formatted and removed typological error from manuscript.

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