

Preparation and Evaluation of Dual Drug Delivery Tablet of Paracetamol and Ibuprofen by using Polymers HPMC, Eudragit, and Guar Gum, Urea and PEG4000

Bojja Saideep¹, Sindhe Sai Karthik¹, Sunkari Komali¹, Sunki Krupavathi¹,
Uppari Shivakumar¹, Chandrasekhara Rao², Sushma Desai³

¹Student, Department of Pharmaceutics, Chilkur Balaji College of Pharmacy, Hyderabad, Telangana, India.

²Professor & Principal, Department of Pharmaceutics

Chilkur Balaji College of Pharmacy, Hyderabad, Telangana, India.

³Research Scholar, Department of Pharmaceutics, Chilkur Balaji College of Pharmacy, Hyderabad, Telangana, India.

Abstract: A Dual drug delivery system formulation is one of the strategies of Novel drug delivery system intended to deliver drug release in two different delivery mechanism one as immediate release and other as controlled or sustained or targeted release of either of a single drug or two different drug to achieve stability and avoid drug interaction enhancing patient compliance. In this project we intended to study the polymer release behavior of drugs paracetamol and Ibuprofen drug where paracetamol formulated as immediate release and ibuprofen formulated as a controlled release polymer as separated formulation. the tablets were prepared by the wet granulation method using HPMC, Eudragit, and guar gum, urea and PEG4000 excipients before compression the powder was evaluated for flow properties and the Invitro dissolution studies revealed guar gum formulation showed a very good controlled release effect with 70.5% at the end of 4 h.

Keywords: Dual drug delivery paracetamol, ibuprofen, HPMC, Guar gum, urea, PEG4000, bilayer tablets..

I. INTRODUCTION

The dual drug delivery is an advanced pharmaceutical technology in which two active pharmaceutical ingredients are combined in single dosage form. In these systems one drug released immediately while other release-controlled manner. often through the polymers like urea, guar gum, or other matrix systems when administered these allows as one drug act rapidly while other release gradually. As a result, the current approach improves bioavailability and efficacy.

IMPORTANCE

A dual drug delivery system is important because it delivers two drugs in single dosage form, making the treatment more effective convenient. It improves the patient compliance by reducing the dosing frequency. This system provides different drug release patterns, where drug released immediately to produce a rapid therapeutic effect while the other is released in sustained manner to maintain the drug concentration for a longer duration. As a result it improves the bioavailability, reduce side effects, and enhances overall therapeutic efficacy. dual drug delivery combination therapy.

DRUGS SUITABLE FOR DUAL DRUG DELIVERY SYSTEM WITH ITS CATEGORY

1 Captopril and hydrochlorothiazide – Hypertension



- 2 Metformin and sitagliptin – Diabetes
- 3 Metformin and Gliclazide – Diabetes
- 4 Aspirin and clopidogrel – prevention of heart attack
- 5 Ramipril and Hydrochloride – treatment
- 6 Ipratropium Bromide and salbutamol – Acute bronchospasm in Asthma COPD
- 7 Salbutamol +and Budesonide

S.NO	Brand name	Active Ingredients	Tablet	Company/Manufacturer	Price ₹
1	Cobmiflam	Ibuprofen 400 mg +paracetamol	Tablet	Sanofi India Ltd	45-55(20 tablets)
2	Combinam	Ibuprofen 400 mg +paracetamol 325mg	Tablet	Mankind pharma Ltd	22-26(10 tablets)
3	Ibufyl plus	Ibuprofen 400 mg +paracetamol 325mg	Tablet	Leeford Healthcare Ltd	25(20 tablets)
4	Buflam plus	Ibuprofen 400 mg +paracetamol 325mg	Tablet	Generic formulation	10-12(10 tablets)
5	Dualfla	Ibuprofen +paracetamol	Tablet	Bactolac Formulations Pvt.Ltd	38-53(10 tablets)
6	Ibunaitp	Ibuprofen +paracetamol	Tablet	Nait pharmaceuticals	45-50(10 tablets)
7	Kriam pharma Tablet	Ibuprofen 400 mg +paracetamol 325mg	Tablet	SRK Puremed LLP	54-60(20 tablets)
8	Chymoday-DP	Diclofemac potassium +paracetamol +Trypsin chymotrypsin	Tablet	Cure Day Health Care Pvt. Ltd	1320(10×10 tablets pack)
9	M plus Duo Bilayer	Diclofenoac 50mg+Paracetamol 325 mg	Tablet	Prolific Consumer Health Care	40 per unit (bulk supply)

TABLE 1 Marketed products of dual drug delivery systems

TABLE 2 Polymer class and its concentration usage in tablet formulation.

POLYMER CLASS	POLYMER	TYPICAL CONCENTRATION
Natural	Guar gum	19-30%
Natural	Xanthan gum	2-20%
natural	Chitosan	2-20%
Semi-synthetic	Ethyl cellulose	5-20%
Semi-synthetic	Hydroxy propyl cellulose	2-15%
Synthetic	Eudragit	5-30%
Synthetic	Carbopol 934	0.5-5%

PARACETAMOL

Paracetamol has a molecular weight 151.16 g/mol. It is sparingly in water and classified as an analgesic and antipyretic drug. Paracetamol relieves, pain and fever by acting on the central nervous system. It inhibits cyclooxygenase (COX) ENZYMES, thereby decreasing the synthesis of prostaglandins. The reduction in prostaglandin synthesis helps to relieve pain, while the reduction in prostaglandins synthesis is helps to relieve pain. While the reduction in postanoids in the hypothalamus lowers fever. Paracetamol has an oral bioavailability of approximately 63-89% .it is metabolized



predominantly in the liver . the onset action is approximately 30-60 minutes after oral administration and 5-10 minutes after intravenous administration. It is primarily excreted through the kidneys

IBUPROFEN

Ibuprofen is a non-steroidal has a molecular anti- inflammatory drug (NSAID). It has a molecular weight of 206.28g/mol. It is less soluble in water but highly soluble in organic solvents such as ethanol. The pKa of Ibuprofen is approximately 4.9, indicating that is a weak acid. The solubility of ibuprofen is approximately 0.02 **mg/ml** in water at room temperature. However, its solubility increases drug becomes ionized. It has highly solubility in ethanol and poly ethylene glycol (**PEG4000**) due to the lipophilic in nature. Ibuprofen reversibly inhibits COX-1 and COX-2 enzymes, reducing prostaglandin synthesis and there by relieving pain and inflammation, and fever. The bio availability of ibuprofen ranges 80-100%. And protein binding is approximately 98-99%. Ibuprofen undergoes hepatic metabolism, mainly through the oxidation by CYP2C9, and metabolites are excreted primarily through the kidneys. The usual oral dosage ranges from 200-400mg depending on the indication.

POLYMERS

UREA: Urea has a molecular weight of 60.06 g/mol.it is a white crystalline compound it is odorless, its highly soluble in water, hygroscopic and has a neutral Ph it is used as plasticizer, pore-forming agent, solubility enhancer it is Hydrophilic additive, plasticizer pore forming agent

POLYETHYLENE GLYCOL (4000): Poly ethylene glycol 4000 has average molecular weight of approximately 3,500 -4,500 **g/mol**. It is classified as hydrophilic polymer, plasticizer, and pharmaceutical excipient. It's a white, waxy solid or flake and is odorless it is soluble in water and alcohol and is hydrophilic .it is used as a tablet binder, lubricant and plasticizer

HPMC: HPMC has a molecular weight ranging from approximately 10,000 to 1,500,000 **g/mol**, depending on the grade .it is widely used as controlled release polymer .it is a white to cream-coloured, odourless powder. It forms clear gel when dispersed in water. It is biocompatible

EDUDRAGIT: Eudragit is a synthetic polymer. Its molecular weight varies depending on the grade such as RS OR RL .it is a white or slightly off-white powder .it is insoluble in water but allows controlled water permeability .it is chemically stable under normal storage conditions it is used as controlled release film coating matrix forming polymer Specific category: Hydrophobic polymer, controlled release polymer, and film forming agent

GUAR GUM: Guar gum is a natural polysaccharide obtained from the guar beans. Its molecular weight is high and varies naturally it is a white to cream-coloured, odourless .it swells and forms a viscous gel in cold water. It is stable under normal conditions and is bio degradable. It is use as a binder, thickening agent, gelling agent, and release-retarding polymer specific category natural hydrophilic polymer, binder, and sustained release polymer. We hypothesized that polymer Eudragit, guar gum and HPMC can be used for studying dual drug delivery system

II. MATERIALS

Paracetamol and ibuprofen were obtained from yarrow chem products, Mumbai, Maharashtra. India hydroxyl propyl methyl cellulose (HPMC E5 LV), METHYL CELLULOSE (4000CPS), guar gum powder, polyvinyl pyrrolidone (pvpk-30), magnesium stearate, and starch (maize) were procured from MOLYCHEM, Mumbai, Maharashtra, India. Urea was procured from RANKEM(AVANTOR), Dehradun, UTTARAKHAND, India. Polyethylene glycol 4000(PEG4000LR) was procured from SD Fine-CHEM Ltd., Mumbai, Maharashtra, India. All the chemicals and excipients used in formulation were analytical reagent (AR) grade and were used as received without further purification.



III. METHODOLOGY

Preparation of calibration curve of paracetamol with pH 6.8 phosphate buffer

Accurately, 100 mg of paracetamol was weighed and transferred into suitable volumetric flask. 5ml of methanol was added, and mixture was stirred until the drug completely dissolved, forming clear solution. Then 5ml of pH 6.8 buffer was added to prepare stock solution for the preparation of primary stock solution, 1ml of primary stock solution was transferred into volumetric flask, and 9ml of PH of buffer was added. for preparation secondary solution, 1ml of the primary stock solution was transferred volumetric flask and 9ml of pH 6.8 phosphate buffer was added. For preparation of the tertiary stock solution, 1ml of secondary stock solution was transferred into volumetric flask, and 9ml of pH 6.8 phosphate buffer was added. Different concentrations of working standard solution were prepare from the territory stock solution by taking 1ml, 2ml, 3ml and 4ml of territory stock solution and added 9ml, 8ml, 7ml and 6ml of ph6.8 phosphate buffer, respectively.

Preparation of calibration curve of paracetamol in 1N HCL

Accurately, 100 mg of paracetamol was weighed and transferred into a suitable volumetric flask. 5 ml of methanol was added, and the mixture was stirred until the drug completely dissolved, forming a clear solution. 5 ml of pH 1N HCL was added to prepare the stock solution. For the preparation of the primary stock solution, 1 ml of the secondary stock solution was transferred into a volumetric flask and 9ml of pH 1N HCL was added. For the preparation of the secondary stock solution, 1ml of the primary stock solution was transferred into a volumetric flask, and 9 ml of pH 1N HCL was added. For the preparation of the territory stock solution, 1 ml of the secondary stock solution was transferred into a volumetric flask, and 9 ml of pH 1N HCL was added. Different concentrations of working standard solutions were prepared from the territory stock solution by taking 1 ml, 2 ml, 3 ml, and 4 ml of the territory stock solution and adding 9 ml, 8ml, 7ml and 6ml of 1N HCL, respectively.

Preparation of calibration curve of Ibuprofen in 1N HCL

Accurately, 100 mg of ibuprofen was weighed and transferred into a suitable volumetric flask. 5 ml of methanol was added, and the mixture was stirred until the drug completely dissolved, forming a clear solution. Then, 5 ml of 1N HCL was added to prepare the stock solution. For the preparation of the primary stock solution, 1 ml of the stock solution was transferred into a volumetric flask, and 9ml of 1N HCL was added. For the preparation of the secondary stock solution 1ml of the primary stock solution was transferred into volumetric flask, and 9ml of pH 6.8 HCL was added. for the preparation of territory stock solution. 1ml of the secondary stock solution was transferred into a volumetric flask, of 1N HCL was added. different concentration of working standard solution were prepared from the territory stock solution by taking 1ml, 2ml, 3ml and 4ml of the territory stock solution and adding 9ml, 8ml, 7ml, and 6ml of 1N HCL respectively

Preparation of calibration curve of Ibuprofen in pH 6.8 phosphate buffer

Accurately transferred 100mg ibuprofen was weighed and transferred into a suitable volumetric flask. 5ml of methanol was added, and the mixture was stirred until the drug completely dissolved, forming a clear solution. then 5ml of 6.8 phosphate to prepare the stock solution. For preparation of primary stock solution, 1ml of the stock solution was transferred into a volumetric flask, and 9ml of pH 6.8 buffer was added. for the preparation of secondary stock solution, 1ml of the primary stock solution was transferred into a volumetric flask and 9ml of pH 6.8 phosphate buffer was added. For preparation of the territory stock solution, 1ml of secondary stock solution was into a volumetric flask, and 9ml of PH 6.8 phosphate buffer was added. different concentration of working standard solution were prepared from the territory stock solution by taking 1ml, 2ml, 3ml and 4ml of the territory stock solution and add 9ml, 8ml, 7ml and 6ml of PH 6.8 phosphate buffer, respectively.



Preparation of paracetamol granules

Accurately weighed 100 mg of paracetamol, 100 mg of starch, 50 mg of methyl cellulose were thoroughly mixed using mortar pestle. then, 5ml of water was added, and mixture was blended well. The wet mass was mixed continuously for 5 minutes. The prepared granules were dried at 60° for 15 minutes. After drying, the dried granules were triturated in mortar finally added 0.5 mg of talc and 0.5 mg of magnesium stearate, powder mass was passed through a sieve to obtain fine granules.

Table 3 Working formula for paracetamol

S.No	Ingredient	F1	F2	F3	F4	F5
1	paracetamol	100	100	100	100	100
2	Starch maize	100	100	100	100	100
3	Methyl cellulose	50	50	50	50	50
4	Talc	0.5	0.5	0.5	0.5	0.5
5	Magnesium stearate	0.5	0.5	0.5	0.5	0.5
6	Poly vinyl pyrrolidone	0.5	0.5	0.5	0.5	0.5

Preparation of Ibuprofen granules

Accurately weighed 100mg of ibuprofen, 25mg of starch, 25mg of methyl cellulose, 0.5mg of talc 0.5 mg of magnesium stearate, and 0.5 mg polyvinyl pyrrolidone were thoroughly mixed used mortar and pestle. Urea polymer was added to powder mixture and blended uniformly. the required quantity of organic color was added gradually to the powder mixture and mixed continuously for 5 minutes. The prepared granules were dried at 60° for 15 minutes. After drying, the dried granules were triturated in mortar finally added 0.5 mg of talc and 0.5 mg of magnesium stearate, powder mass was passed through a sieve to obtain fine granules.

Table 4 Working formula for Ibuprofen

INGREDIENTS	F1	F2	F3	F4	F5
IBUPROFEN	100	100	100	100	100
POLYMER AMOUNT	UREA 100	GUARGUM 100	HRDROXY PROPYL METHYL CELLOUSE 100	EUDRAGIT 100	POLY ETHYLENE GLYCOL 100
STARCH	25	25	25	25	25
METHYL ELLULOSE	25	25	25	25	25
TALC	0.5	0.5	0.5	0.5	0.5
MAGNESIUM STRETE	0.5	0.5	0.5	0.5	0.5
POLYVINYL PYRROLIDONE	0.5	0.5	0.5	0.5	0.5

Preparation of dual drug delivery system tablets

Accurately weigh the quantity of the drug both paracetamol and ibuprofen 1:1 ratio. The ibuprofen formulated with a different polymer the adjusting the tablet punching dye 500mg. In the half compression paracetamol punched. In second half compression ibuprofen is punched out now, we can notice the bi-layered dual drug.

PHYSICAL EVALUATION TABLET

1. PRE-COMPRSESION STUDIES

Angle of repose: The angle of repose was measured using the fixed funnel method to assess the flow properties of the ibuprofen, paracetamol. These was allowed to flow freely through a funnel onto a flat surface until a conical heap was



formed. The height (h) and radius (r) of powder heap measured and angle of repose was calculated using the equation $\tan \theta = h/r$

2. Post-Compression Studies

Physical evaluation tests are essential to ensure the quality, uniformity, and mechanical strength of tablets of pharmaceutical formulations

1. Thickness and diameter

The thickness and diameter of a tablet were measured by using digital Vernier caliper's measured were recorded and the average values were calculated

2. Hardness:

Hardness of a tablet was determined using a hardness tester. the force required to break each tablet was measured and average hardness value was recorded

3. Weight variation Test

The twenty tablets are collected are weighed collectively and individually from collective weight the average weight was calculated. the percent weight variation was calculated by using formulae 1.

Percentage of weight variation = (average weight - individual weight)/ average weight 100-----(1)

4. In -vitro dissolution studies

In these dissolutions test the drug percentage was determined at different time intervals using 1 N HCL for the initial 60 minutes, followed by the phosphate buffer (pH 6.8). after 60 minutes in 1 N HCL, the drug release was recorded for all formulations. subsequently the dissolution medium was changed to phosphate buffer (pH 6.8) and drug release was measured at 120,150 and 180 minutes. the percentage drug release was recorded for the urea, guar gum eudragit, HPMC, PEG 4000 and marketed formulation.

5. Drug stability studies

All the prepared formulations were subjected to stability studies according to ICH guidelines of safety and quality parameters under the different storage conditions. the samples were stored at cool temperature, cold temperature, warm temperature (30- 40°C) and hot temperature (50) the formulations were observed for changes in color, hardness, caking, softening, dis-colouration, surface melting and other physical characteristics.

IV. RESULTS & DISCUSSION

Table 5 Calibration curve values of paracetamol drug in 1N HCL

S. no	Concentration (ug/ml)	Absorbance (nm)
1	blank	0 nm
2	1ml	0.100nm
3	2ml	0.248nm
4	3ml	0.397nm
5	4ml	0.694nm



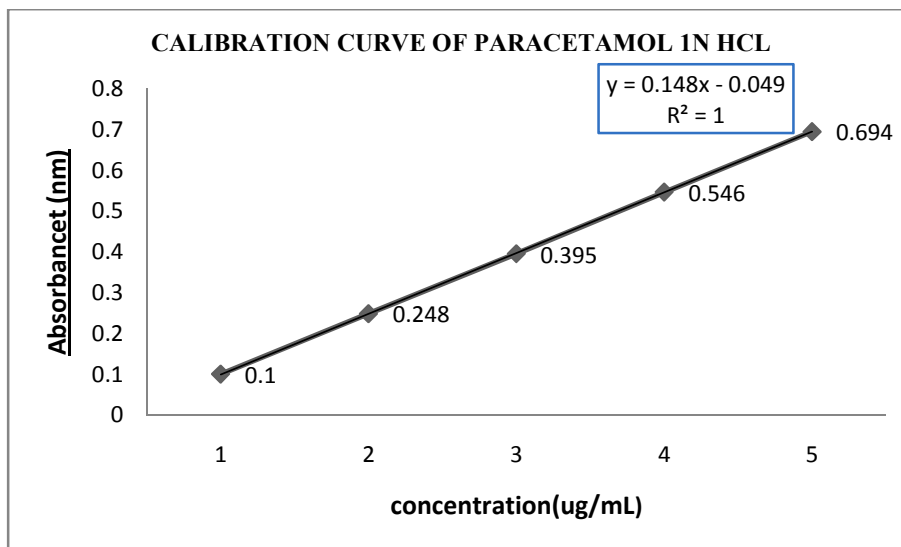


Fig 1 Calibration graph of paracetamol drug in 1N HCL

Table 6 Calibration curve values of paracetamol drug in 6.8 pH phosphate buffer

S. no	Concentration (ug/mL)	Absorbance(nm)
1.	1ml	0.56
2	2ml	0.1
3	3ml	0.248
4	4ml	0.395

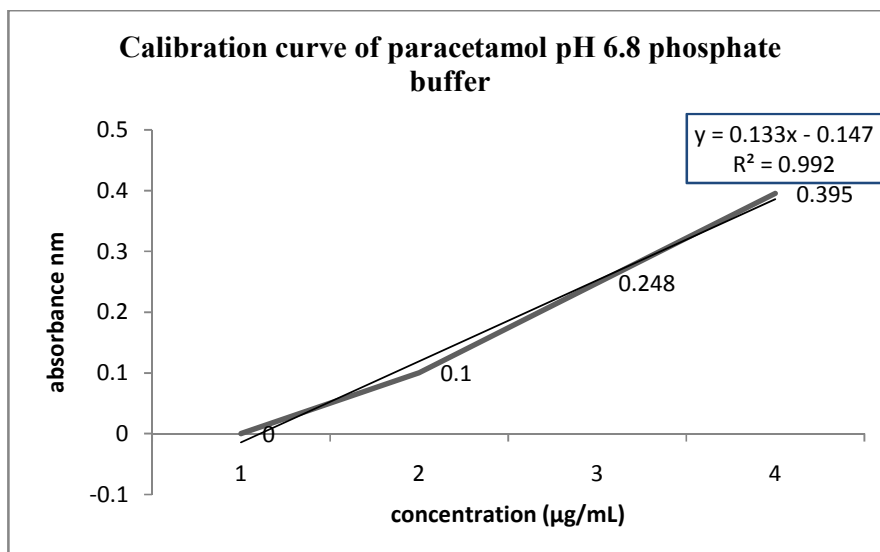


Fig 2 Calibration graph of paracetamol drug in 6.8 pH phosphate buffer



Table 7 Calibration curve values of Ibuprofen drug in 1N HCL

S. no	Concentration(ug/mL)	Absorbance(nm)
1	1ml	0.414
2	2ml	0.630
3	3ml	0.747
4	4ml	1.142

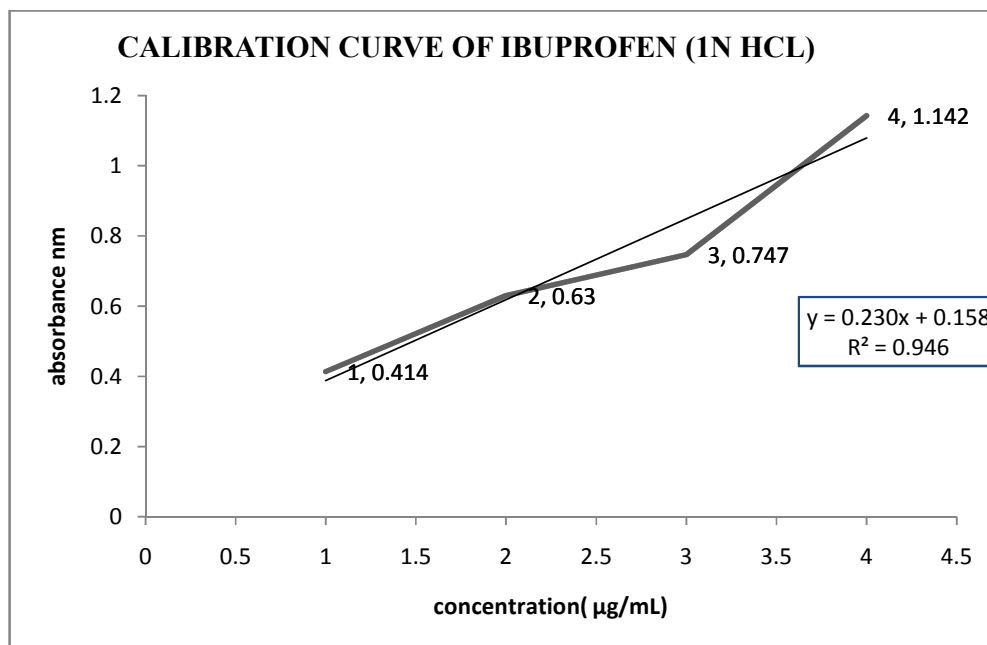


Fig 3 Calibration graph of Ibuprofen drug in 1N HCL

Table 8 Calibration curve values of Ibuprofen drug in 6.8 pH phosphate buffer

S. no	Concentration (ug/mL)	Absorbance (nm)
1	1ml	0.395
2	2ml	0.719
3	3ml	0.911
4	4ml	1.297



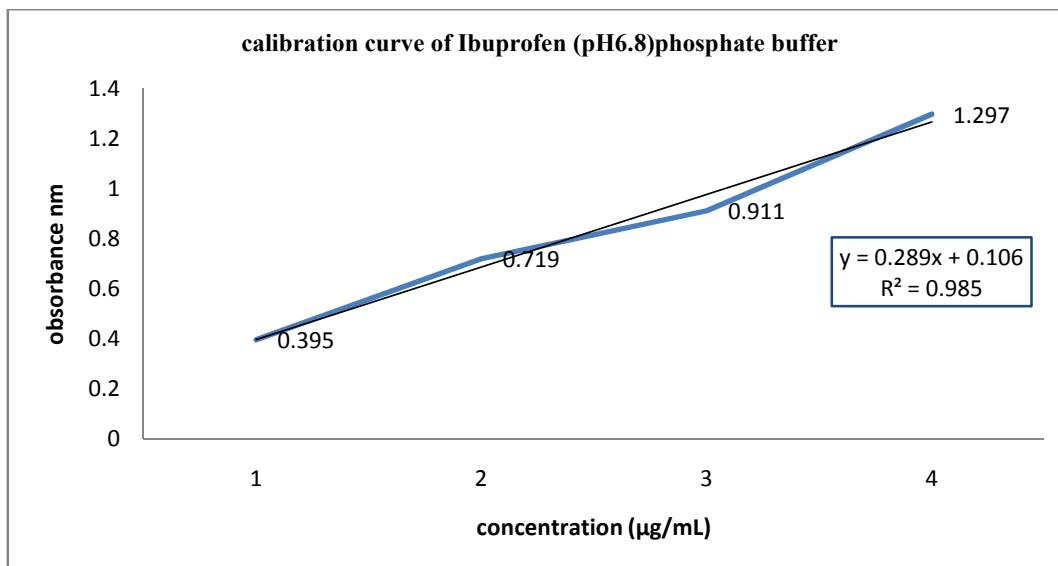


Fig 4 Calibration graph of Ibuprofen drug in 6.8 pH phosphate buffer

Table 9 Pre-compression Angle of Repose parameter

SAMPLE	TRAIL 1(°)	TRAIL 2(°)	TRAIL 3(°)	S.D
Paracetamol Granules.	24.70	25.17	25.25	25.28±0.65
Ibuprofen Granules	30.9	33.7	33.9	32.89±1.64

s.d= standard deviation

paracetamol exhibited excellent flow properties. while ibuprofen shows the good flow characteristics. both powders are suitable for the tablet compression.

DISSOLUTION TEST STUDIES

The drug release percentage over time are at 60 min, urea showed a release of 0.10%, while the marketed product release was 36.3%.the other formulations are intermediate release Values guar gum released 8.2% eudragit release 13.3%, HPMC released 25.2% and 0.6% PEG4000.By 150 minutes the release percentage urea released 52.4% guar gum54.6%, eudragit 54.4% HPMC 55.1% PEG 4000 55.3% and the marketed product 53.7%.By 180 minutes the release levels stabilized urea 0.8% guar gum0.96% ,eudragit 1.1%, HPMC 1.04% PEG 4000 1.1 % and the marketed product 1.9%.Finally ,at 220 minutes , urea released 1.7% , guar gum 1.4%, eudragit 0.5% HPMC 2.6% peg 4000 1.23% and the marketed product 2.1%.The marketed product had a high initial release but showed relatively low release at time points, indicating the burst release pattern. the formulations containing polymers like guar gum, eudragit, HPMC, PEG 4000 exhibited more controlled sustained release over time these results highlight how different polymer compositions influence the drug release profile in system

Table 10 Drug release percentage with various polymers used in dual drug delivery system

TIME (min)	UREA	EUDRAGIT	GUAR GUM	HPMC	PEG4000	MARKETED PRODUCT
60	0.10%	8.2%	13.3%	25.2%	16.3%	36.3%
90	1.18%	1.44%	1.24%	0.014%	0.6%	0.61%



120	15.4%	34.6%	24.4%	45.1%	55.3%	35.7%
150	26.7%	52.6%	40.9%	54.5%	41.7%	43%
180	38.5%	72.7%	53.3%	64.1%	51.2%	54%
210	50.8%	90.96%	61.1%	71.04%	61.1%	61.9%
240	71.7%	95.4%	70.5%	82.6%	71.23%	72.1%

STABILITY STUDIES

The stability test conducted for ibuprofen and paracetamol tablets under various conditions yielded the following characteristics

1. cool temperature

Ibuprofen tablet showed no change in color and no caking indicating good stability at cool temperature. Paracetamol tablet also exhibited no change in colour or hardness, demonstrating stability under similar conditions

2. Cold temperature

Both ibuprofen and paracetamol tablets showed no change in their physical appearance, suggesting stability at cold temperatures

3. Hot

Ibuprofen tablets showed surface melting upon observation, indication sensitivity to high temperature 50°C

Paracetamol tablets displayed slight yellowing after 3 weeks, suggesting some degree of thermal degradation

4. Warm

Ibuprofen tablets exhibited slight softening and no discoloration, indicating minor physical changes but overall stability. Paracetamol tablets remained unchanged fully complying with stability criteria. Ibuprofen tablets are stable up to 40° C exhibit physical changes at higher temperatures. Paracetamol tablets are stable up to 50°C are protected from the light, but show signs of degradation at 50°C, such as yellowing, both formulations are stable under standard storage conditions but require protection from elevated temperature to prevent physical and chemical changes. the observed changes at higher temperature highlight the importance of appropriate storage conditions to maintain drug efficacy and safety.

Table 11 Drug Stability studies of formulations F1-F5

S.NO	Temperature	Parameter	F1	F2	F3	F4	F5
1	COOL 4-25°	Colour	No Change	No Change	No Change	No Change	No Change
		Physical Stability	No Change	No Change	No Change	No Change	No Change
2	COLD 4°	Colour	No Change	No Change	No Change	No Change	Light Brown
		Physical Stability	Moisture Absorbed	Moisture Absorbed	Moisture Absorbed	Moisture Absorbed	No Change
3	WARM 30-40°	Colour	No Change	No Change	No Change	No Change	No Change
		Physical	No	No	No	No	Moisture



		Stability	Change	Change	Change	Change	Absorbed
4	HOT 40°	Colour	Brown Colour	Brown Colour	Brown Colour	Brown Colour	No Change
		Physical Stability	No Change	No Change	No Colour	No Change	Chipping

Summary

The present study was carried out to develop a dual drug delivery system of paracetamol and ibuprofen using different polymers, namely Urea (F1), Guar Gum (F2), Eudragit (F3), HPMC (F4), and Polyethylene Glycol (F5). The calibration curves of both drugs demonstrated a direct relationship between concentration and absorbance, confirming that the UV spectrophotometric method was suitable for the quantitative estimation of the drugs during dissolution studies. The in-vitro drug release study showed that the polymer selected for the formulation significantly influenced the release profile of ibuprofen. In the acidic medium (1 N HCl), the marketed product exhibited a higher initial drug release than the prepared formulations, indicating a faster release in the gastric environment. After changing the dissolution medium to phosphate buffer (pH 6.8), all formulations showed a gradual increase in drug release with time. Among the prepared formulations, Guar Gum (F2) exhibited the highest cumulative drug release at the end of the dissolution study, whereas HPMC (F4) produced a more controlled and sustained release profile. The differences in drug release behavior may be attributed to the swelling, hydration, and matrix-forming properties of the polymers, which regulate drug diffusion from the tablet. Overall, the study demonstrated that polymer selection plays a vital role in controlling drug release and maintaining formulation stability in a dual drug delivery system. The developed formulations exhibited satisfactory drug release characteristics and acceptable stability, indicating their potential for sustained drug delivery. Among the formulations evaluated, Guar Gum (F2) showed the highest cumulative drug release, while HPMC (F4) provided a controlled release pattern, suggesting that both polymers are suitable for developing an effective dual drug delivery system.

V. CONCLUSION

In this project aimed at polymer performance especially controlled release behavior of various polymers guar gum, a natural polymer found to show good controlled effect on drug Ibuprofen in the dual drug delivery system. The formulation was optimized for its flow properties during Pre-formulation studies and Invitro Dissolution studies suggesting a good polymer fit for dual drug release systems.

REFERENCES

- [1]. Zhang Y, Li P, Sun F, et al. Recent advances in dual-responsive drug delivery systems for cancer therapy. J Control Release. 2020;325:358-76.
- [2]. Wang J, Wei Q, Xu Y, et al. Dual-drug delivery systems based on hydrogel-nanoparticle composites. Mater Today. 2021;45:120-35.
- [3]. Chen H, Wang J, Shi J. Nanotheranostics for dual drug delivery and imaging in cancer. Biomaterials. 2019;216:119284.
- [4]. Li M, Liu C, Wang H, et al. Stimuli-responsive dual-drug release systems in biomedicine. Chem Soc Rev. 2022;51(12):4856-902.
- [5]. Zhao N, Tan A, Li X, et al. Co-delivery of anti-cancer drugs using polymeric micelles. J Control Release. 2021;338:234-55.
- [6]. Liu Y, Li Y, Wang C, et al. Dual drug-loaded liposomes for overcoming multidrug resistance. Int J Pharm. 2020;586:119561.
- [7]. Huang X, Zhang X, Sun H, et al. Advances in dual-release drug delivery systems for oral administration. Expert Opin Drug Deliv. 2021;18(5):601-18.



- [8]. Patel M, Sharma A, Kumar R. Dual-phase extended-release tablets: formulation strategies and evaluation. *J Drug Deliv Sci Technol.* 2022;71:103328.
- [9]. Park K. Controlled drug delivery systems: past, present, and future. *J Control Release.* 2014;190:3-8.
- [10]. Torchilin VP. Multifunctional and stimuli-responsive nanocarriers for cancer therapy. *Nat Rev Drug Discov.* 2014;13(11):813-27.
- [11]. Jiang X, Wang Y, Deng X. Biodegradable polymers for dual drug release systems. *J Mater Chem B.* 2021;9(35):7140-58.
- [12]. Xu D, Zhao Y, Li J, et al. Dual-drug loaded mesoporous silica nanoparticles for targeted therapy. *ACS Nano.* 2019;13(9):10245-58.
- [13]. Singh S, Gupta R, Kumar P. Polymeric micelles for dual-drug delivery in combating multidrug resistance. *Nanoscale.* 2020;12(41):21102-18.
- [14]. Kim S, Lee J, Park H, et al. Dual-stimuli responsive hydrogels for controlled drug delivery. *Biomater Sci.* 2022;10(2):345-60.
- [15]. Wang Q, Zhang L, Chen X, et al. Stimuli-responsive dual-drug delivery systems: pH, temperature, and redox. *Adv Sci.* 2021;8(14):2100876.
- [16]. Zhang H, Wang X, Liu Z, et al. Dual-drug co-delivery systems for synergistic treatment of bacterial infections. *ACS Appl Mater Interfaces.* 2022;14(8):10012-25.
- [17]. Gupta A, Jain A, Singh V. Dual-release formulations of solid oral dosage forms. *AAPS PharmSciTech.* 2020;21(7):256.
- [18]. Chen Y, Huang X, Li Z, et al. Layer-by-layer assembly for dual drug delivery systems. *Chem Eng J.* 2021;426:131234.
- [19]. Lee H, Kim M, Park S, et al. Dual-targeted and dual-drug loaded liposomes for cancer therapy. *Theranostics.* 2019;9(23):6985-7002.
- [20]. Li T, Wang J, Liu Y, et al. Stimuli-responsive multi-stage drug delivery systems for dual-drug release. *Adv Healthc Mater.* 2020;9(15):2000672.
- [21]. Zhang W, Li N, Chen J, et al. Dual drug-loaded polymeric nanoparticles for combination chemotherapy. *Int J Nanomedicine.* 2021;16:5421-38.
- [22]. Kumar R, Singh P, Sharma S, et al. Recent trends in dual-drug release systems for bone tissue engineering. *J Biomed Mater Res A.* 2021;109(8):1305-22.
- [23]. Liu J, Chen Z, Wang H, et al. pH-responsive dual-drug delivery systems for tumor therapy. *Macromol Biosci.* 2020;20(6):2000080.
- [24]. Wang P, Li H, Zhang Y, et al. Dual-drug codelivery nanosystems: an emerging approach for reversing multidrug resistance. *Pharmacol Ther.* 2022;230:107955.
- [25]. Zhao X, Zhang X, Li Z, et al. Dual-functionalized nanoparticles for dual-drug delivery. *Small.* 2021;17(35):2101345. Zhao X, Zhang X, Li Z, et al. Dual-functionalized nanoparticles for dual-drug delivery. *Small.* 2021;17(35):2101345.
- [26]. Patel H, Singh K, Sharma R, et al. Recent advances in dual-release oral drug delivery systems. *Expert Opin Drug Deliv.* 2022;19(2):145-62.
- [27]. Chen F, Wang C, Li X, et al. Dual-stimuli responsive nanocarriers for precise drug delivery. *Nano Today.* 2021;39:101223.
- [28]. Yang B, Liu Y, Zhang S, et al. Dual-drug loaded hydrogels for local and systemic delivery. *J Control Release.* 2022;345:15-32.
- [29]. Wu J, Li Y, Wang Z, et al. Dual-drug codelivery based on polymer-lipid hybrid nanoparticles. *Acta Biomater.* 2020;115:240-55.
- [30]. Li J, Zhang Y, Liu C, et al. Dual-drug release systems in inflammation and tissue repair. *Biomaterials.* 2022;285:121528.

