Formulation and Evaluation of pH Sensitive Polymeric Nanosuspension Containing Rabeprazole and Amoxicillin

Aman Kumar Singh*[1], Umesh P. Singh[2], Mohd. Faizan[3], Ram Sevak Verma[4]

[1,2,3]Department Of Pharmaceutics, Rameshwaram Institute of Technology and Management, Lucknow 227202, Uttar Pradesh, India.

[4]J. S. Singh Institute of Pharmacy. Sitapur Uttar Pradesh-261207, India

***Corresponding Author:**

Department Of Pharmaceutics

Rameshwaram Institute of Technology and Management

Lucknow 227202, Uttar Pradesh, India.

E-Mail Address: *aman12singh.19@gmail.com*

Tel: *8303561136, 6391289155*

ABSTRACT

Rabeprazole is a PPI used in treatment of gastro oesophageal reflux disease and other condition like Peptic ulcer, hyper acidity etc and Amoxicillin is an antibiotic used to treat various infection and disease caused by bacteria. Both of these are used together in treatment of peptic ulcer caused due to H.Pylori infection but there is a lack of liquid oral dosage form of rabeprazole in combination with Amoxicillin. The aim of the study was formulation and evaluation of pH-sensitive polymeric nanosuspension loaded with amoxicillin and rabeprazole. The precipitation method was used in the preparation of the nanosuspension. The properties of RAB/AMOXY loaded polymeric nanosuspension, such as particle size, loading capacity, encapsulation efficiency, and drug release pattern, were significantly impacted by variations in the polymer: drug ratio. According to in-vitro drug release results, formulation F3 has the highest percentage of drug release over the specified time, while formulation F5 exhibits the greatest amount of drug release delay. Drug release pattern according to Zero order drug release was demonstrated by Formulation. The formulation F3 has the best drug entrapment efficiency, with 92% of the drug captured in the polymer, according to the drug entrapment efficiency test. The particle's nano size range was verified by the SEM and Zeta sizer findings in which formulation F3 shows particle size of 156 nm and zeta potential of 15.8 Mv. The drug polymer compatibility investigation using FTIR spectra demonstrated the compatibility of drugs RAB and AMOXY with polymers EL-100 and ES-100. The DSC result indicates that the drug's properties have changed in the formulation and that the drug and excipient do not interact. Formulations with a pH of less than 6.5 are stable because basic pH causes nanoparticles in antisolvents to dissolve. The short-term stability investigation validates the long-term stability during storage and shows no change in drug entrapment efficiency and drug release pattern from polymer.

KEY WORDS: Nanosuspension, Peptic Ulcer, Proton pump Inhibitor, Enteric Coating, Eudragit L-100, Eudragit S-100.

INTRODUCTION

Proton pump inhibitors:

Proton pump inhibitors (PPIs) is a class of drug that lowers the production of gastric acid. They function by Inhibiting the proton pumps of parietal cell in stomach lining, which secrets acid into the stomach. Proton pumps, or the hydrogen/potassium adenosine triphosphatase enzyme system, are blocked by proton pumps inhibitor in the stomach parietal cells. This inhibition lowers the amount of hydrogen ions secreted into the stomach lumen, which lowers the generation of gastric acid[1]. When there is an issue with excessive stomach acid production, PPIs are frequently recommended[2]. This involves treatment for GERD, or gastric reflux disease, erosive esophagitis recovery, peptic ulcer therapy (duodenal and stomach ulcers), preventing NSAID-induced stomach ulcers. Proton pump inhibitors include medications such as rabeprazole, pantoprazole, lansoprazole, omeprazole, and esomeprazole. Oral administration of PPIs is common, usually once per day. They're mostly taken before meal[3].

Nanosuspension:

The introduction of nanotechnology has caused a revolution in the field of pharmaceutical sciences, especially with the creation of nanosuspensions. When it comes to medication delivery, nanosuspensions are state of the art and have many advantages over conventional formulations. Submicron-sized medication particles are suspended in an aqueous solution stabilized using polymers or surfactants. With the use of this technology, poorly water-soluble medications now have more options for increasing their bioavailability, solubility, and therapeutic efficacy[4].

Colloidal dispersions of nanoscale particles in a liquid media are known as nano-suspensions. Surfactants stabilise the minuscule drug particles in nanosuspensions, a particular kind of therapeutic preparation. These are mainly composed of drug particles with a particle size of less than 1µm mixed with an antisolvent (probably water). The size of the particles in nano-suspensions typically ranges from 1 to 500 nanometres[5]. A major obstacle in the field of pharmaceutical formulation has been the restricted water solubility of numerous medications, resulting in inadequate body absorption and bioavailability. By bringing drug particle sizes down to the nanometer range—typically less than 1 µm—nanosuspensions solve this problem. For preperation of nanosuspensions, two different methods are used: "Bottom-up process technology" and "Top-down process technology." For example, bottom-up procedures assemble smaller components into more complex structures, while top-down methods slice or mill bigger material portions to generate smaller units. Notably, drugs made with nanosuspension techniques include atorvastatin, nabilone, and griseofulvin[6].

Rabeprazole Sodium:

Rabeprazole is a PPI. Other than different PPIs on the market, rabeprazole is a novel substituted benzimidazole proton pump inhibitor that has a number of unique features. Rabeprazole binds covalently to the proton pump (H+/K+-ATPase) in the stomach parietal cell, rendering it inactive resulting in rise in the pH of the stomach and gastric acid production is inhibited[7].

Amoxicillin:

Amoxicillin belongs to penicillin class of antibiotic, widely prescribed for its efficacy against a range of bacterial infections. The mode of action of amoxicillin is inhibiting bacterial cell wall synthesis. It works by binding to penicillin-binding proteins, thereby dameging bacterial growth and leading to cell death[8].

MATERIAL AND METHOD

Material:

Amoxicillin was purchased from N.V.D. Scientific PVT Ltd. Lucknow, India and Rabeprazole was received as gift sample from Akums PVT Ltd. Haridwar India. All other chemicals were of analytical grade purchased from local suppliers.

Physical Property Testing:

In physical property test different parameter like organoleptic property (Colour, Odour, Taste ets), Melting point and solubility testing was done.

Determination of λmax and Standard curve preparation:

Using phosphate buffer, a 1% w/v solution of rabeprazole and amoxicillin both was produced, and the λmax was calculated by scanning the solution for maximal absorbance in a UV Spectrophotometer between the 200–400 nm range[9]. To make the initial stock solution, 100 mg of Rabeprazole and Amoxicillin both were precisely weighed and diluted in 100 ml of Phosphate Buffer. To make II stock solution, 10 milliliters of the aforesaid solution were taken and diluted to 100 milliliters using the same solvent. The stock solution II aliquot quantity was further diluted with phosphate buffer to obtain drug concentrations of 5µg, 10µg, 15µg, 20µg, and 25µg per milliliter of the final solution. Next, using phosphate buffer as a blank, the absorbance was measured in a UV spectrophotometer at 200-400 nm. Plotting absorbance vs concentration was done on the graph[10].

Compatibility Study Using FTIR:

Using an FTIR, infrared spectroscopy was performed, and the spectrum was collected between 4000 and 400 cm^{-1}. Through the observation of any shift in the drug's peaks in the spectrum of the physical mixture of drug, the reaction between the drug and the excipients was seen via IR-spectral studies[11].

Preparation of Nanosuspension:

The nanosuspension containing Rabeprazole and Amoxicillin was prepared using precipitation method. For preparation of nanosuspension Drugs (RAB and AMOXY) dissolved in methanol which forms the organic phase. Tween 80 (used as surfactant) and pH sensitive polymer (EL-100 and ES-100) were dissolved in water to form antisolvent as aqueous phase. Drug solution is added drop wise in antisolvent under magnetic stirring. Nanoparticles are formed spontaneously. The preparation is placed on magnetic stirrer for 3h and then in ultracentrifuge at 20000 RPM and supernatant is discarded, replaced with antisolvent and particle are resuspended with the help of sonication. By varying the ratio of polymer six different formulation were prepared by above mentioned method. Different evaluation parameters were prepared performed on prepared formulation[12].

Fig 1 Different NS Formulation of Rabeprazole and Amoxicillin

Table: 1 Different NS Formulation of Rabeprazole and Amoxicillin

Formulation	Rabeprazole (mg)	Amoxicillin (mg)	Eudragit L-100 (mg)	Eudragit S-100 (mg)	Tween – 80 (ml) (v/v)
F1	5	125	130		2%
F2	5	125	260		2%
F3	5	125	390		2%
F4	5	125		130	2%
F5	5	125		260	2%
F6	5	125		390	2%

Evaluation of Nanosuspension

a) **Mean Particle size:** The produced nanosuspension's mean particle size and size distribution (polydispersity index) were evaluated with Zetasizer, also known as photon correlation spectroscopy (PCS), which is based on the law of light diffraction. The samples were suitably diluted with water to a reasonable intensity of scattering and re-dispersed by shaking before to the measurement[12].

b) **Zeta Potential:** The electric charge at the particle surface is measured by the Zeta potential, which shows the physical stability of colloidal systems. Aqueous dispersions exhibit long-term electrostatic stability when their zeta potential values are in range ±30mV. Using Zetasizer, the electrophoretic mobility of the particles was determined in order to evaluate the Zeta Potential in this investigation[3].

c) **Entrapment Efficiency:** The produced nanosuspension was ultracentrifuged in order to assess the free drug or EE content. The amount of free drug in the clear supernatant was then quantified using UV spectroscopy Bose et al. [11]. The determination of individual free drug concentration in nanosuspension *Simultanious equation method* is used[3].

d) **In vitro Drug release:** Using the dialysis bag diffusion technique, different nanosuspension formulations were released in vitro. After the sac was hermetically sealed, pH 7.4 phosphate buffer was added, and any leaks were drained. Within the receptor compartment was 100 mL of pH 7.4 phosphate buffer, which was kept at 37±0.50C with a magnetic stirrer spinning at 500 rpm. Aliquots of 1 mL were taken out at predetermined intervals and replaced right away with the same volume of brand-new pH 7.4 phosphate buffer. The UV Spectroscopy was used to measure the amount of medication emitted[13].

e) **Kinetic Analysis of Release Data:** To better understand the drug release mechanism, the results of an in vitro drug release study of nanoparticles were fitted with a range of kinetic equations, including Higuchi's model (cumulative % drug release vs. square root of time), zero order (cumulative % release vs. time), and first order (log % drug remaining vs. time). R2 values were calculated for the linear curve that the aforementioned plots showed[4].

f) **Electron microscopy:** Using SEM, the surface properties of lyophilized nanosuspensions of all formulation were examined. The samples were placed on double-sided carbon adhesive tape that had been fastened to brass stubs beforehand. A sputter coater was then used to provide a gold coating to the samples, utilizing a 10-mA process current for four minutes[7].

g) **DSC Characterization:** By measuring melting point temperatures and the corresponding enthalpies, DSC can be used to identify the kind and speciation of crystallinity present in nanoparticles. DSC analysis was performed on the pure RAB, AMOXY, Eudragit L-100, Eudragit S-100, and generated NPs.

h) **Stability Study:** Stability tests were conducted for the final optimized nanosuspension over a Three-month period. In order to measure the extent of entrapment efficiency and invitro drug release, the temperature was kept at 40 ºC/75% RH[4].

RESULTS

Solubility testing:

Solubility of both drugs i.e. Rabeprazole and Amoxicillin were tested in different solvents.

Table: 2 Solubility of Rabeprazole and Amoxicillin

Sr.No	Solvent	Rabeprazole Sodium	Amoxicillin Trihydrate
1.	Water	Insoluble	Insoluble
2.	Methanol	Soluble	Soluble
3.	Ethanol	Soluble	Soluble
4.	Dilute acid	Insoluble	Soluble
5.	Dilute Base	Insoluble	Soluble
6.	Acetone	Soluble	Insoluble
7.	Chloroform	Insoluble	Insoluble
8.	Benzene	Insoluble	Insoluble

Melting point determination:

It was found that the melting point of Amoxicillin trihydrate was 199.6 ºC and that of Rabeprazole sodium was 140.3 ºC.

Evaluation of organoleptic properties:

The physical attributes of Rabeprazole sodium and Amoxicillin trihydrate were shown in table 3.1.2 (A) and 3.1.2 (B) respectively-

Table: 3 Physical property of Rabeprazole sodium

Characteristics	Observation	
	Rabeprazole	Amoxicillin
Material	Powder	Powder
Colour	Pale Yellow	White
Odour	No odour	No odour
Taste	Slightly Bitter	Slightly Bitter

Determination of λmax:

The λmax of both drug were determined using UV spectroscopy. The λmax of Rabeprazole was found to be 275 nm and that of amoxicillin was found to be 225 nm.

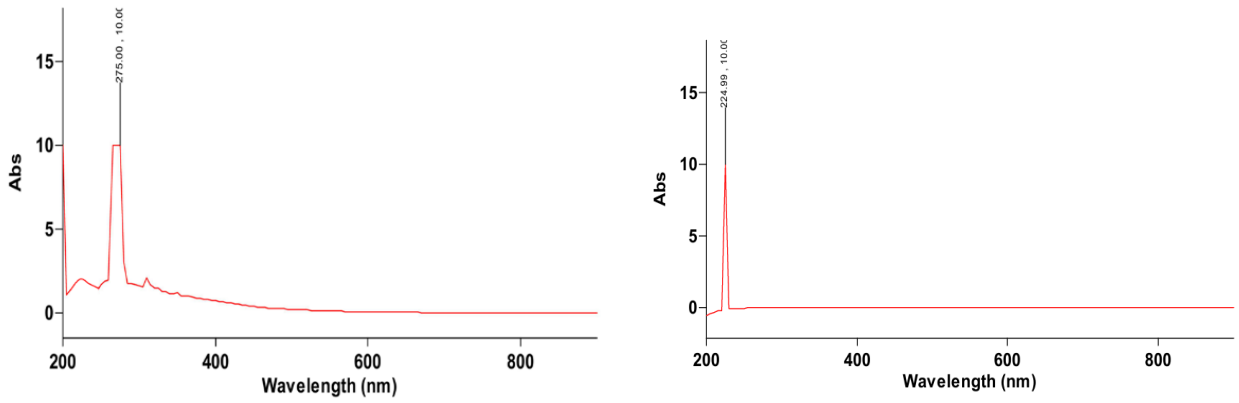


Fig : 2 λmax of Rabeprazole Sodium and Amoxicillin

Calibration Curve of Rabeprazole Sodium and Amoxicillin:

Table 3.1.5.1 show the data obtained for Calibration data of Rabeprazole sodium and Amoxicillin in 6.8 pH Phosphate buffer solution. The absorbance as found in the range of 0.071 to 0.439 and 0.046 to 0.405 for Rabeprazole sodium and Amoxicillin respectively by plotting the data, a regressed straight line was obtained with the R^2 value 0.9969 and 0.9951 for Rabeprazole sodium and Amoxicillin respectively which shows the good correlation between the data points. The data shows that the Rabeprazole sodium and Amoxicillin follow the Beer Lamberts law in the concentration range of 5 to 25 µg/ml.

Table: 4 Calibration data of Rabeprazole sodium in phosphate buffer

Sr.No	Concentration (µg/ml)	Absorbance	
		Rabeprazole	Amoxicillin
1.	5	0.071	0.046
2.	10	0.143	0.125
3.	15	0.247	0.231
4.	20	0.348	0.336
5.	25	0.439	0.405

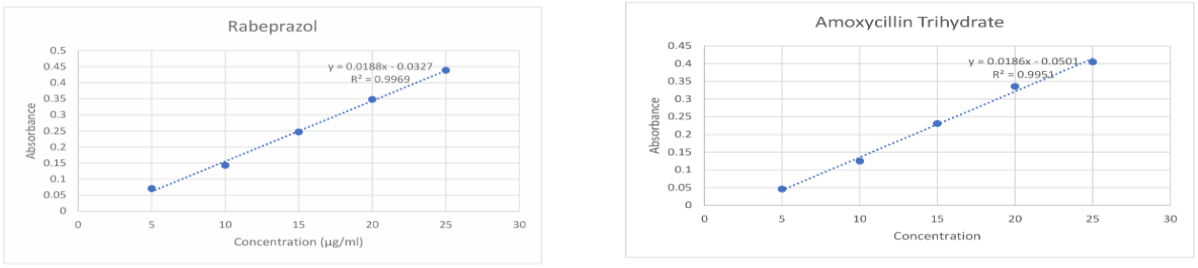


Fig: 3 Calibration Curve of rabeprazole Sodium

Drug excipient compatibility study using FTIR:

Analyzing individual chemical spectra is crucial for predicting compatibility between compounds using IR (infrared) spectra. This stage allows you to observe any peak shifts, intensity changes, or the appearance of additional peaks after the chemicals have been mixed. Compatibility or incompatibility may become apparent based on these changes. The FTIR spectra of the medication amoxicillin trihydrate, rabeprazole sodium, and their physical combination with polymers were acquired, and spectral peaks were observed between 4000 cm-1 and 400 cm-1. As all peaks are present in physical mixture spectra it shows no interaction between drugs and polymer and shows compatibility.

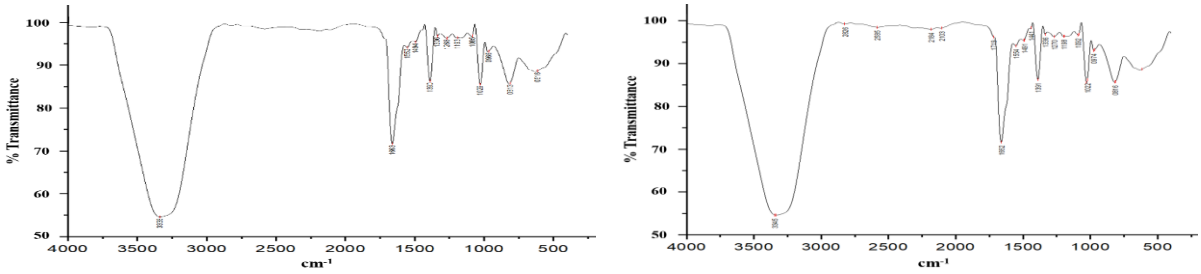


Fig: 4 (A) FTIR Spectra of Rabeprazole and Amoxicillin

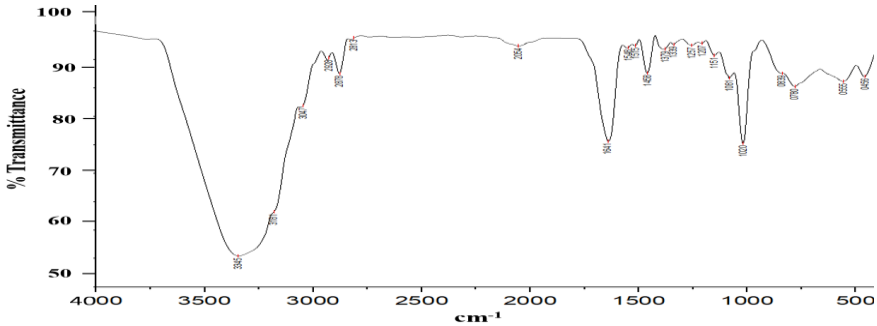


Fig: 4 (C) FTIR Spectra of Drug and Polymer Mixture

EVALUATION OF FORMULATION

Mean Particle size and Zeta Potential

The size of droplets in nanosuspension batches could be affected by concentration and type of the polymer used. The particle size distribution of formulation ranged from 156 to 425 nm. Notably, the nanosuspension formulated with Eudragit L-100 (F3) exhibited the smallest particle size at 156 nm. This demonstrates the potential for achieving smaller particle sizes using Eudragit L-100. The formulation F3 shows minimum size range i.e. 156 nm and formulation F 5 shows maximum size range i.e. 425 nm.

The zeta potential of a nanoparticle is a crucial indicator of its surface charge and stability. Higher zeta potential values lead to stronger repulsion forces between particles, enhancing the stability of nanosuspension. Notably, Formulation F 3 exhibits an impressive zeta potential of 15.8.

Table : 5 Mean Particle Size of Different Formulation

Formulation Code	Mean Particle Size (nm)	Zeta Potential (mv)
F 1	255	10.1
F 2	258	9.8
F 3	156	15.8
F 4	321	8.2
F 5	425	-2.9
F 6	381	-8.9

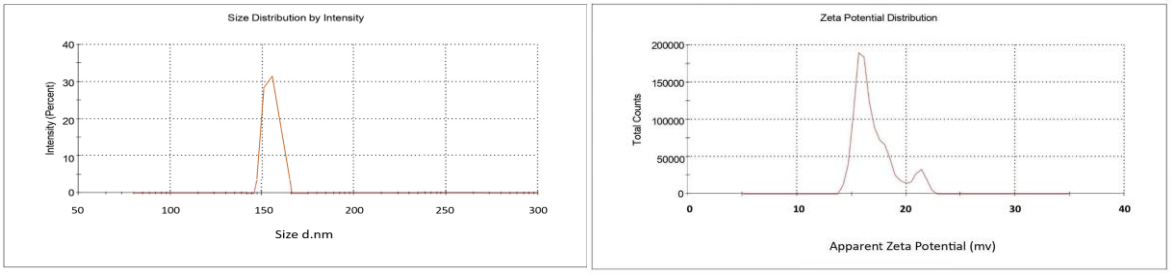


Fig : 5 Particle Size Distribution of (A) F1 (B) F2 (C) F3 (D) F4 (E) F5 (F) F6

Entrapment Efficiency:

The formulations showed between 79 and 92% drug entrapment. Formulation F 3, specifically, attained the maximum entrapment of 92.3%. Moreover, formulations with Eudragit L-100 demonstrated better entrapment than formulations with Eudragit S-100. The results have been shown in Table 3.2.3

Table : 6 EE of Different Formulation

Formulation Code	Entrapment Efficiency (%)
F 1	82.4
F 2	87.1
F 3	92.3
F 4	79.3
F 5	85.8
F 6	91.6

In vitro drug release:

The drug release statistics for all batches of RAB and AMOXY loaded nanosuspensions revealed a wide range of 68.7-88.76%. In study it was found that the quantity of polymer has direct impacts on the release of medication in formulations. The F3 formulation displayed a notably higher and faster in vitro drug release in compare to other formulations.

Table : 7 % drug release of Different Formulation

Time (min)	Drug Release (%)					
	F 1	F 2	F 3	F 4	F 5	F 6
0	0	0	0	0	0	0
15	22.58	22.99	23.58	22.27	21.92	20.03
30	39.84	40.82	42.33	39.12	37.85	32.6
45	57.64	58.96	59.05	56.84	51.08	49.94
60	72.36	73.25	73.78	72.21	64.46	59.97
90	85.71	86.39	88.76	83.56	71.54	68.7

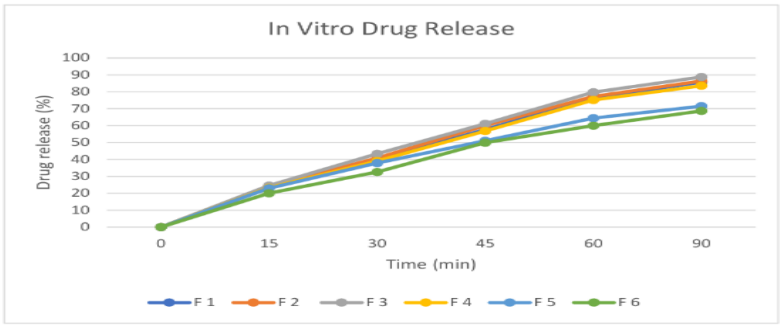
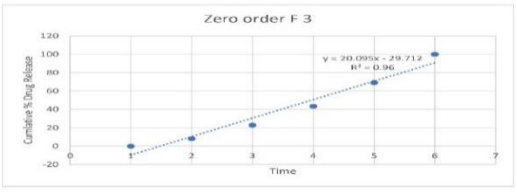
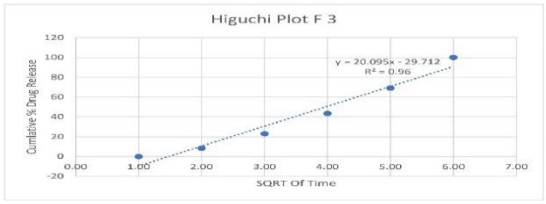


Fig : 6 % Drug Release of Different Formulation

Release kinetics:

The data of drug release is used to plot different release kinetics. The zero order R^2 value of formulations found to be maximum hence the formulations were found to obeys zero order kinetics.





Electron Microscopy (SEM):

SEM of all nanosuspension formulation was done to analyze the morphological characteristic of formulation. SEM analysis shows that particle of all formulations are of spherical shape and the size of formulation are in nanometer range.

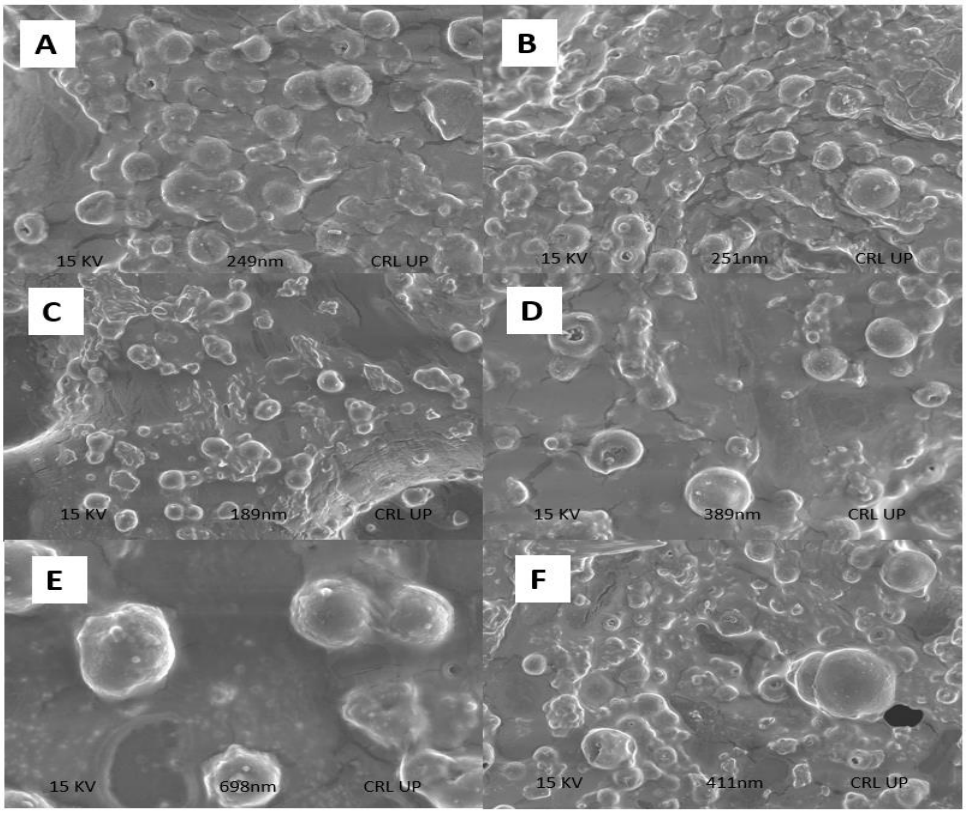


Fig : 7 SEM of (A) F1 (B) F2 (C) F3 (D) F4 (E) F5 (F) F6

Differential scanning calorimetry (DSC) characterization:

DSC is an essential method for examining nanoparticle crystallinity. To confirm drug polymer compatibility DSC is used. We delved into the thermal behavior of drugs, polymers, and drug-loaded nanoparticles. Any significant changes in the thermal behavior of the drug or polymer could signal a potential interaction between the substances. Additionally, heating curves in DSC were graphed based on temperature (C) and enthalpy (m/w).

At 143 ºC, rabeprazole sodium exhibited a melting endotherm, which was followed by the medication degrading. Amoxicillin trihydrate's thermogram displayed a peak at 198 ºC. Eudragit L-100 and Eudragit S-100 polymers displayed peaks at 155 and 157 ºC, respectively as shown in. fig 3.2.7

These findings shows no interaction between the drug and polymer, and that the properties of the two substances were unchanged. The mixture of drugs and polymers was uniform.

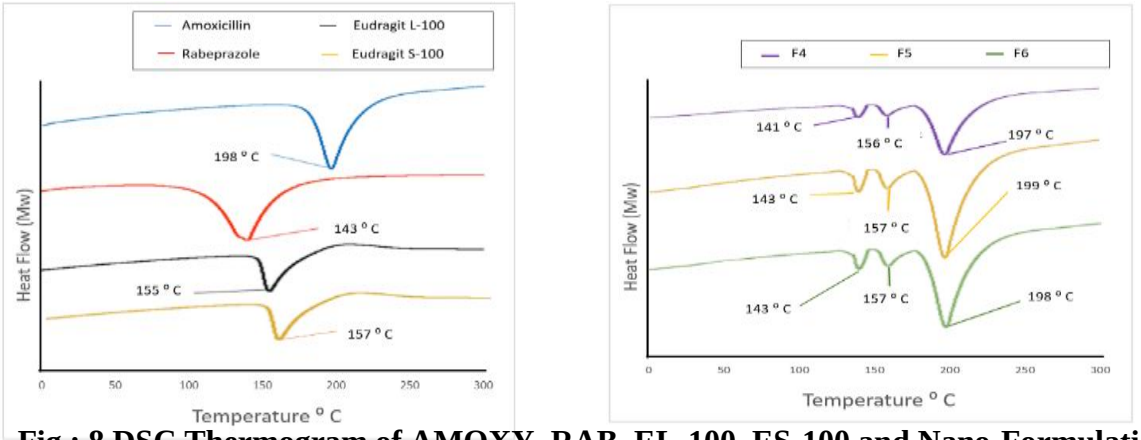


Fig : 8 DSC Thermogram of AMOXY, RAB, EL-100, ES-100 and Nano-Formulations

Short Term Stability Study:

For three months, the optimized formulation F 3 was maintained at 40 ºC/75% RH for stability testing. After 1 month, the formulation shows minor change in drug entrapment efficiency and drug release from the original formulation. After three months the formulation is again checked for entrapment efficiency and % drug release which shows a minor change from initial value. The in vitro drug release investigation showed very little variation. Before and after study the formulation's R2 values were 0.9558, 0.9488 and 0.9301 respectively. Therefore, the R2 value differed by very little. After study, the overall release was discovered to be 83.61%. The results of the stability analysis indicate that neither the entrapment efficiency nor the in vitro drug release pattern have changed significantly. As such, the medication was deemed appropriate for storage.

Table : 8 Short Term Stability Testing Data

Condition	Entrapment Efficiency	Invitro Drug Release				
		15 Min	30 Min	45 Min	60 Min	90 Min
Initial	92.3	23.58	42.33	59.05	73.78	88.76
40 C / 75 % RH (1 Month)	91.8	22.63	41.81	58.38	73.98	86.49
40 C / 75 % RH (3 Month)	90.9	24.32	44.16	56.49	74.89	83.61

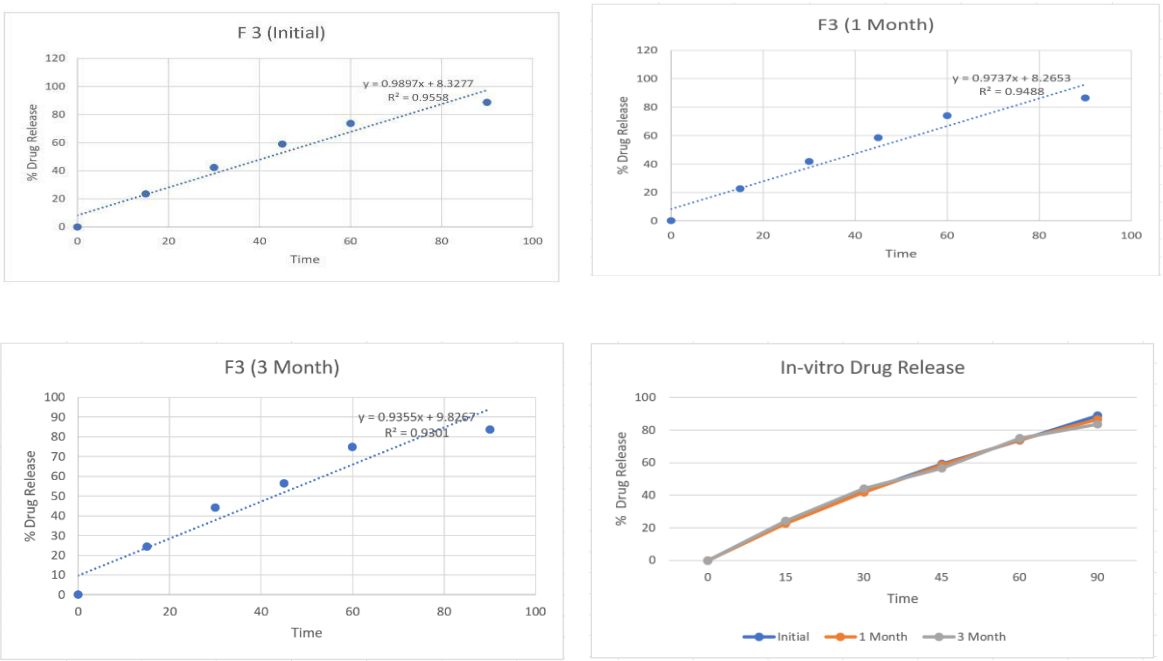


Fig : 9 Stability Testing Data

CONCLUSION

The formulation F3 has the best drug release percentage over the specified period, while formulation F5 exhibits the greatest drug release delay, according to in-vitro drug release results. Drug release pattern following zero order drug release was shown by Formulation. The formulation F3 has the best drug entrapment efficiency, with 92% of the drug intraped in the polymer, according to the drug entrapment efficiency test. The particle's nanosized range was verified by the Zetasizer findings F3 has best particle size with 156 nm with 15.8 mV zeta potential. The drug polymer compatibility investigation using FTIR spectra demonstrated the compatibility of drugs RAB and AMOXY with polymers EL-100 and ES-100. The DSC result indicates that the drug's properties were not changed in the formulation and that the drug and excipient do not interact. pH of all formulations is less than 6.5 which shows the stability of nanosuspension. The short-term stability investigation validates the long-term stability during storage and shows a small change in drug entrapment efficiency and drug release pattern from polymer. Furthermore, it can also be concluded that these studies are not sufficient to determine the efficacy of formulation prepared, it requires more studies and work.

REFERENCES

1. Agarwal V, Bajpai M., **“**Preparation and Optimization of Esomeprazole Nanosuspension using Evaporative Precipitation– Ultrasonication”, Tropical Journal of Pharmaceutical Research, no (2014):497-503
2. Aldosari BN, Ibrahim MA, Alqahtani Y, Amal El Sayeh F. “Formulation and evaluation of Fluconazole Nanosuspensions: In vitro characterization and transcorneal permeability studies”. Saudi Pharmaceutical Journal. 2024 May 16:102104.
3. Bakheit A.H., Al-Kahtani H.M., Albraiki S., “Rabeprazole: A comprehensive profile. Profiles of Drug Substances, Excipients, and Related Methodology”, no (2020):137-183.
4. Bendas ER, Abdelbary AA. Instantaneous enteric nano-encapsulation of omeprazole: pharmaceutical and pharmacological evaluation. International journal of pharmaceutics. 2014 Jul 1;468(1-2):97-104.
5. Chingunpituk J. “Nanosuspension technology for drug delivery. Walailak Journal of Science and Technology (WJST)”. 2007;4(2):139-53.
6. Chinthaginjala H, Abdul H, Reddy AP, Kodi K, Manchikanti SP, Pasam D. “Nanosuspension as Promising and Potential Drug Delivery: A Review”. 2020. Int J Life Sci. Pharm Res. 2020;11(1):P59-66
7. Diefenthaelera SH, Bianchinb MD, Marquesc MS, Nonnenmacherd JL, Benderd ET, Benderd JG, Neryd SF, Cichotad LC, Külkamp-Guerreiro I., **“**Omeprazole nanoparticles suspension: Development of a stable liquid formulation with a view to paediatric administration”, International Journal of Pharmaceutics, no (2020):589-599.

8. Gupta MK, Sreedharan SK, Sajeeth CI. “Design development and characterization of omeprazole loaded nanosuspension.” Journal of Pharmaceutical Negative Results. 2022 Nov 5:1195-208.
9. Gupta MK, Sreethu K. Sreedharan, Sajeeth CI., “Design, Development and characterization of omeprazole loaded nanosuspension”, Journal of Pharmaceutical Negative Results, no (2022):1198-1208.
10. Gupta, Aditya, and Gurdeep Singh. “Formulation and evaluation of rabeprazole sodium delayed release tablets”. Am. J. PharmTech Res 10 (2020): 114-127.
11. Li W, Yang Y, Tian Y, Xu X, Chen Y, Mu L, Zhang Y, Fang L. “Preparation and in vitro/in vivo evaluation of revaprazan hydrochloride nanosuspension”. International journal of pharmaceutics. 2011 Apr 15;408(1-2):157-62.
12. Mehetre, Gautam D., Rameshwar S. Cheke, and Vinayak N. Shrikhande. “Formulation and in-vitro evaluation of enteric coated tablet incorporating rabeprazole.” Journal of Drug Delivery and Therapeutics 10.2-s (2020): 50-57.
13. Nasef A.M., Gardouh R.A., Ghorab M.M.., “Formulation and in-vitro evaluation of pantoprazole loaded pH-sensitive polymeric nanoparticles”. Future Journal of Pharmaceutical Sciences, no (2017): 103-117.
14. Rani A, Verma R, Kumar M, Tiwari A, Tiwari V, Bhatt S, Mittal V, Kaushik D. “Nanosuspension as a Novel Nanovehicle for Drug Delivery: A Recent Update on Patents and Therapeutic Applications.” Current Nanomedicine (Formerly: Recent Patents on Nanomedicine). 2024 Jul 1;14(2):88-98.
15. Sampathi S, Haribhau CJ, Kuchana V, Junnuthula V, Dyawanapelly S. “Nanosuspension encapsulated chitosan-pectin microbeads as a novel delivery platform for enhancing oral bioavailability.” Carbohydrate Polymers. 2023 Nov 1;319:121177.
16. Shah R, Soni T, Shah U, Suhagia BN, Patel MN, Patel T, Gabr GA, Gorain B, Kesharwani P. “Formulation development and characterization of lumefantrine nanosuspension for enhanced antimalarial activity.” Journal of Biomaterials Science, Polymer Edition. 2021 May 3;32(7):833-57.
17. Shanika LGT, Reynolds A, Pattison S, Braund R., “Proton pump inhibitor use: systematic review of global trends and practices”. European Journal of Clinical Pharmacology, no (2023):1159-1172.
18. Sheikh A., Asati S., “Preparation, evaluation and optimization of solid lipid nanoparticles composed of pantoprazole”,Journal of Drug Delivery and Therapeutics, no(2022): 12-18
19. Solanki, Kinjal P., et al. Formulation and Evaluation of Sublingual Tablets of Rabeprazole Sodium using Bioadhesive Polymers." International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN) 13.3 (2020): 4932-4941.
20. Sun M, Gao Y, Pei Y, Guo C, Li H, Cao F, Yu A, Zhai G. “Development of nanosuspension formulation for oral delivery of quercetin. Journal of biomedical nanotechnology.” 2010 Aug 1;6(4):325-32

21. Sunder S, and Nair R (2016). “Methods of Nanonization of Drugs for Enhancing their Dissolution”. Euro J Adv Engg Tech, 3: 101-110
22. Sutradhar KB, Khatun S, Luna IP. “Increasing possibilities of nanosuspension. Journal of nanotechnology.” 2013 Jan 1;2013
23. Thakral S, Thakral NK, Majumdar DK. Eudragit®: a technology evaluation. Expert opinion on drug delivery. 2013 Jan 1;10(1):131-49.
24. Thattil JG, Kumar KK, and Kumar BD (2018). “Nanosuspension technology in pharmaceuticals.” J Bio Innov 7: 660-677.
25. Yang Q, Tan T, He Q, Guo C, Chen D, Tan Y, Feng J, Song X, Gong T, Li J. “Combined Amphiphilic Silybin Meglumine Nanosuspension Effective Against Hepatic Fibrosis in Mice Model”. International Journal of Nanomedicine. 2023 Dec 31:5197-211.
26. Zuccari G, Alfei S. “Development of phytochemical delivery systems by nano-suspension and nano-emulsion techniques.” International Journal of Molecular Sciences. 2023 Jun 6;24(12):9824