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FORMULATION AND EVALUATION OF NAPROXEN AND PANTOPRAZOLE MULTILAYERED TABLETS

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Keywords:

Naproxen, Pantoprazole, Delayed release, Multi-layered tablets

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ABSTRACT: Naproxen, a non-steroidal anti-inflammatory drug suggested for the long term treatment of disease conditions such as Rheumatoid Arthritis and Osteoarthritis poses an immediate risk of stomach ulceration. To avoid this risk, a proton pump inhibitor is often prescribed along with it. In the present study, Naproxen (500mg) is prepared in combination with Pantoprazole, a proton pump inhibitor as a multi-layer coated tablet. First, Naproxen is prepared as core tablet by wet granulation method. Then it is enteric coated to assist its delayed-release. Over this enteric coated tablet, Pantoprazole (20mg) drug layer is applied to get combination product. The prepared tablets were evaluated for physicochemical properties such as weight variation, hardness, friability, disintegration and drug content. The *in-vitro* drug release studies were conducted for Naproxen core tablets, Naproxen enteric coated tablets and multi-layered tablets in 0.1N HCl and 7.4 pH phosphate buffer. The analytical results obtained at several stages of preparation of the product were found to be satisfactory. The *in-vitro* drug release studies of Naproxen and Pantoprazole from multilayered tablets in 0.1N HCl and 7.4 pH phosphate buffer has shown that the release of drugs follow zero order kinetics.

INTRODUCTION: Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs *via* various pharmaceutical products of different dosage forms. Pharmaceutical products designed for oral delivery are mostly the immediate-release type. Because of their clinical advantages over immediate-release pharmaceutical products containing the same drugs, delayed-release pharmaceutical products have gradually gained medical acceptance and popularity since their introduction into the market place.

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Recently, a new generation of combination pharmaceutical products with one immediate-release component and one delayed-release component have received regulatory approval for marketing [1, 2]. Through such dosage forms several advantages are seen but still some problems arise in preparation of this kind of dosage form such as physical incompatibility, chemical incompatibility etc. Therefore, the bilayer and multilayer tablets are known as a novel drug delivery system.

Arthritis is an inflammation of the joints. It can affect one joint or multiple joints. There are more than 100 different types of arthritis, with different causes and treatment methods. Two of the most common types are osteoarthritis (OA) and rheumatoid arthritis (RA). The most well-known therapy for Arthritis is the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [3, 4].

Naproxen is an NSAID of the propionic acid class, works by reversibly inhibiting both the COX-1 and COX-2 enzymes as a non-selective coxib. But it poses an intermediate risk of stomach ulcers. To reduce stomach ulceration risk, it is often combined with a proton-pump inhibitor to reduce stomach acid production during long-term treatment for those with pre-existing stomach ulcers or for those having history of developing stomach ulcers while on NSAIDs.

Pantoprazole is a proton pump inhibitor drug that inhibits gastric acid secretion. It works on gastric parietal cells to irreversibly inhibit (H+/K+)-ATPase function and suppress the production of gastric acid [5, 6].

Studies showed that NSAID drugs in combination with PPI's significantly reduce the incidence of gastric ulcers, regardless of NSAID dose, in at-risk patients, and is associated with improved UGI tolerability relative to enteric coated NSAID.[1]

Therefore the primary objectives of the study were to develop a suitable dosage form for two active ingredients, NSAID (in the enteric coated layer) and PPI and to overcome the under prescribed combination of these two drugs. In this study, the combination product of Naproxen and Pantoprazole is prepared by using multi-layer tablet coating technology. Naproxen core tablet is prepared by compression and then enteric coated. Upon this enteric coated tablet, Pantoprazole drug layer is applied. The number of ingredients were tried to reduce as much as possible which would make it a cost-effective formulation.

MATERIALS AND METHODS:

Materials: Naproxen and Pantoprazole were obtained as gift samples from Alembic pharmaceuticals Ltd., Gujarat. Hydroxypropyl methylcellulose (Colorcon Asia Pvt Ltd., Goa), Iso propyl alcohol (Rankem, RFCL Ltd., New Delhi), Magnesium oxide (Geocon products, Mumbai), Polyethylene glycol (Gangwal chemicals Pvt. Ltd., Mumbai) and all other chemicals used were of analytical grade.

Methods:

Drug- Excipient Compatibility Studies: Drug-Excipient Compatibility studies were performed using FT-IR spectrophotometer studies.

Preparation of Standard Curve of Naproxen: Calibration curve of Naproxen was prepared in pH 7.4 phosphate buffer. 28 mg of the drug was dissolved in 50 ml of pH 7.4 phosphate buffer. From this 5 ml of solution was taken and diluted to 25ml with phosphate buffer to obtain a stock solution of concentration 0.112 mg/ml. This solution was then serially diluted with phosphate buffer to give solutions of concentration ranging from 20µg/ml to 80µg/ml. The absorbance of these solutions was measured at 332 nm using phosphate buffer as blank and the standard curve was plotted to get the linearity and regression equation.

Preparation of Standard Curve of Pantoprazole: Calibration curve of pantoprazole was prepared in 0.1 N HCl. 10 mg of the drug was dissolved in 100 ml of 0.1N HCl to obtain a stock solution of concentration 100 µg/ml. This solution was then serially diluted with 0.1 N HCl to give solutions of concentration ranging from 5 µg/ml to 25 µg/ml. The absorbance of these solutions was measured at 285 nm using 0.1N HCl as blank and the standard curve was plotted to get the linearity and regression equation

Preparation of Naproxen Core tablets (D_1 - D_5) [7]: Naproxen core tablets were prepared by direct compression method using Tablet Compression Machine (Elite Scientific and Equipments, Guntur). Povidone solution (1:7 ratio) in water was prepared by mixing with a stirrer into a glass vessel. Accurate quantities of Naproxen, diluent and disintegrant were added. Binder solution was added, mixed for 3-4 minutes to prepare wet mass. The wet mass was dried in a Hot air oven at 45°C for about 15 to 20 minutes. The granules were then obtained by rubbing the wet mass with mesh #20 and then collected followed by drying. Magnesium stearate was weighed, sieved through mesh #44 and added to the granules & mixed for 5 minutes. The granules were then compressed to get Naproxen Core tablets given in the **Table 1**.

Subcoating of Naproxen Core tablets: Based on the evaluation results of the core tablets, one formulation was chosen for further coatings. It was performed twice, first on the naproxen core tablets, then on the enteric coated tablets. The subcoating solution is prepared as per the formula given in the **Table 2**.

TABLE 1: FORMULATION OF NAPROXEN CORE TABLET

Name of the material	Quantity (mg / tablet)				
	D_1	D_2	D_3	D_4	D_5
Naproxen	500	500	500	500	500
Povidone	21	10	_	_	_
Microcrystalline Cellulose	_	_	_	21	10
Anhydrous Lactose	_	11	21	_	11
Croscarmellose Sodium	21	21	21	21	21
Magnesium stearate	8	8	8	8	8
Total Quantity	550	550	550	550	550

TABLE 2: FORMULATION OF SUBCOATING SOLUTION

Name of the material	Quantity per tablet
Methanol	0.1 ml
Methylene chloride	0.1 ml
HPMC E15 LV	4 mg

Enteric coating of sub-coated Core tablets [7]: Enteric coating solution was prepared by taking Hydroxypropyl Methylcellulose as coating polymer and other ingredients as shown in the **Table 3**. It is then applied over sub-coated tablets of Naproxen

TABLE 3: FORMULATION OF ENTERIC COATING SUSPENSION

Name of the material	Quantity per tablet
HPMC E15 LV	16 mg
Isopropyl Alcohol	0.2 ml
Purified water	0.2 ml
PEG	0.01 ml

Drug layering: Finally, after subcoating of Enteric coated Naproxen tablets, the drug layering solution containing Pantoprazole is applied to get combination drug product. Five different drug layer formulations ($F_1 – F_5$) were prepared as shown in the **Table 4**.

TABLE 4: FORMULATION OF DRUG LAYERING COATING SUSPENSION CONTAINING PANTOPRAZOLE

Name of the material	F_1	F_2	F_3	F_4	F_5
Pantoprazole	30 mg	30 mg	30 mg	30 mg	30 mg
HPMC E15 LV	18 mg	18 mg	18 mg	18 mg	18 mg
Magnesium Oxide	6 mg	10 mg	_	_	_
Calcium Carbonate	_	_	10 mg	15 mg	_
Calcium Hydroxide	_	_	_	_	6 mg
Isopropyl Alcohol	0.2 ml	0.2 ml	0.2 ml	0.2 ml	0.2 ml
Purified water	0.2 ml	0.2 ml	0.2 ml	0.2 ml	0.2 ml
PEG	0.01 ml	0.01 ml	0.01 ml	0.01 ml	0.01 ml
	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation of preformulation parameters: [7, 8, 9] All the formulations were evaluated for flow properties independently at both pre-granulation and pre-compression stages. The fixed funnel method was employed to measure the angle of repose. Bulk and tapped densities were determined by tapped density apparatus from which compressibility index and Hausner's ratio values were calculated.

Evaluation of Multi-layered tablets: [7, 9]

1. Weight Variation: Ten tablets were selected at random and weighed individually. Average weight was calculated and standard deviation was computed.

2. Hardness: Hardness is termed as the tablet crushing strength and it is the force required to break a tablet diametrically. Hardness of tablets was measured by selecting 5 tablets randomly and the hardness of each tablet was measured with Pfizer hardness tester (Elite Scientific and Equipment, Guntur). It is usually measured in terms of kg/cm^2.

3. Friability: Ten tablets were weighed and placed in the friabilator (Elite Scientific and Equipment, Guntur), which was then operated for 25 revolutions per minute. After 4 minutes, the tablets were dusted and reweighed.

The percentage friability was determined using the formula,

Percentage friability =

[Initial weight - Final weight/Initial weight] × 100

4. Disintegration Time: The disintegration time of the tablets was determined as per Indian pharmacopoeia. The test was carried out using tablet disintegration apparatus (Elite Scientific and Equipments, Guntur). Distilled water was used as a disintegrating media at 35-39 °C. The time required to obtain complete disintegration of all the tablets was noted.

Drug Content: Ten tablets were crushed in a mortar and following procedure carried out.

- **Drug Content for Naproxen:** Preparations equivalent to 20 mg was weighed accurately and transferred to 100ml volumetric flask and dissolved in 7.4 phosphate buffer. The volume was made upto the mark with 7.4 phosphate buffer. Absorbance of the resulting solution was measured at 332 nm using appropriate blank solution. The drug content was estimated using calibration curve.
- **Drug Content for Pantoprazole:** Preparations equivalent to 10 mg was weighed accurately and transferred to 100ml volumetric flask and dissolved in 0.1N HCl. The volume was made upto the mark with 0.1N HCl. Absorbance of the resulting solution was measured at 285 nm using appropriate blank solution. The drug content was estimated using calibration curve.

***In-vitro* Dissolution Studies:** [7, 9] *In vitro* dissolution studies were conducted using Dissolution test apparatus DS 800 (Lab India, Mumbai). The dissolution specifications for all types of tablets tested were given in the table 5. For dissolution of Multi-layered tablets, 0.1N HCl was used as dissolution medium for the first two hours and 7.4 pH phosphate buffer for the remaining time. Samples of 5 mL were withdrawn at predetermined time intervals and replaced with 5 mL of fresh dissolution medium. The collected samples were diluted with dissolution fluid, wherever necessary, and were analyzed for Pantoprazole at 285 nm and Naproxen at 332 nm by using Double beam UV Visible Spectrophotometer SL 164 (Elico, Hyderabad).

TABLE 5: DISSOLUTION SPECIFICATIONS FOR ALL THE TYPES OF TABLETS

Dissolution specifications	Naproxen Core tablet (1)	Naproxen Core tablet (2)	Enteric coated tablet (1)	Enteric coated tablet (2)	Multi-layer tablet (1)	Multi-layer tablet (2)
Dissolution medium	0.1N HCl	pH 7.4 Phosphate buffer	0.1N HCl	pH 7.4 Phosphate buffer	0.1N HCl	pH 7.4 Phosphate buffer
Volume of dissolution medium	900 ml	900 ml	900 ml	900 ml	900 ml	900 ml
Temperature	37 ± 0.5℃	37 ± 0.5℃	37 ± 0.5℃	37 ± 0.5℃	37 ± 0.5℃	37 ± 0.5℃
RPM	50	50	50	50	50	50
Duration	1 hour	1 hour	1 hour	1 hour	2 hours	1 hour

Release Kinetics: [8, 9, 10]

Curve Fitting Analysis:

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as:

1) Cumulative percentage drug released vs. time (*in-vitro* drug release plots)
2) Cumulative percentage drug released vs. Square root of time (Higuchi's Plots)
3) Log cumulative percentage drug remaining vs. time (First order plots)
4) Log cumulative percentage drug released vs. log time (Korsmeyer-Peppas plots)
5) Cube root percentage drug remaining vs. time (Hixon – Crowell)/

RESULTS AND DISCUSSION:

Drug-Excipient Compatibility Studies:

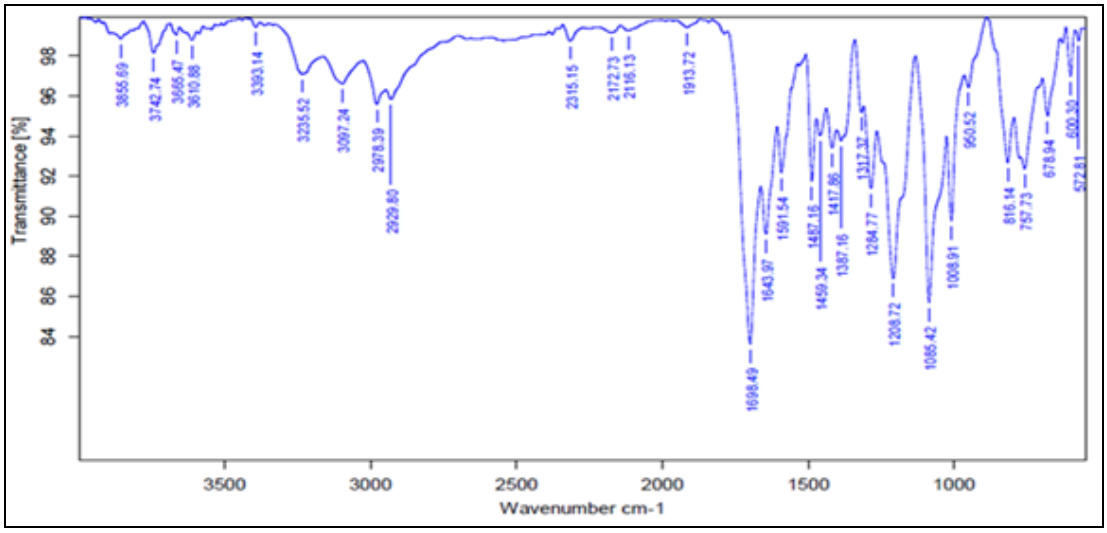

FIG. 1: FT-IR SPECTRA OF NAPROXEN PURE DRUG

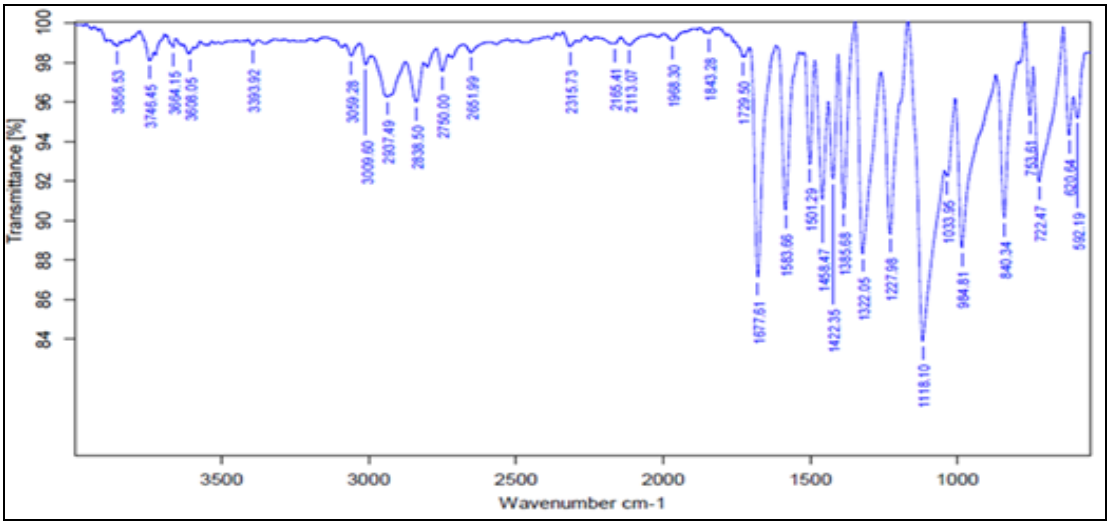

FIG. 2: FT-IR SPECTRA OF NAPROXEN WITH EXCIPIENTS

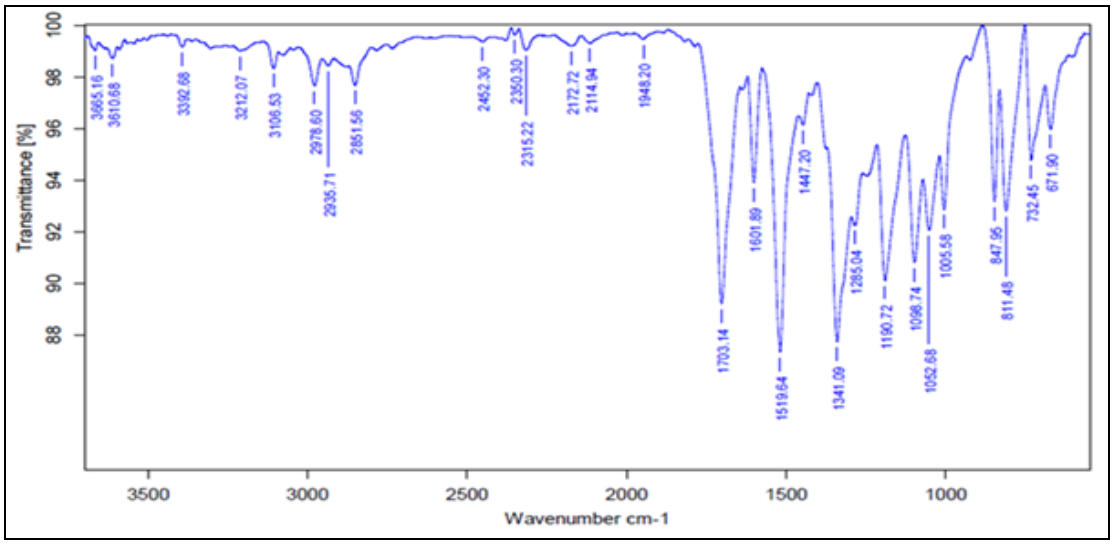

FIG. 3: FT-IR SPECTRA OF PANTOPRAZOLE PURE DRUG

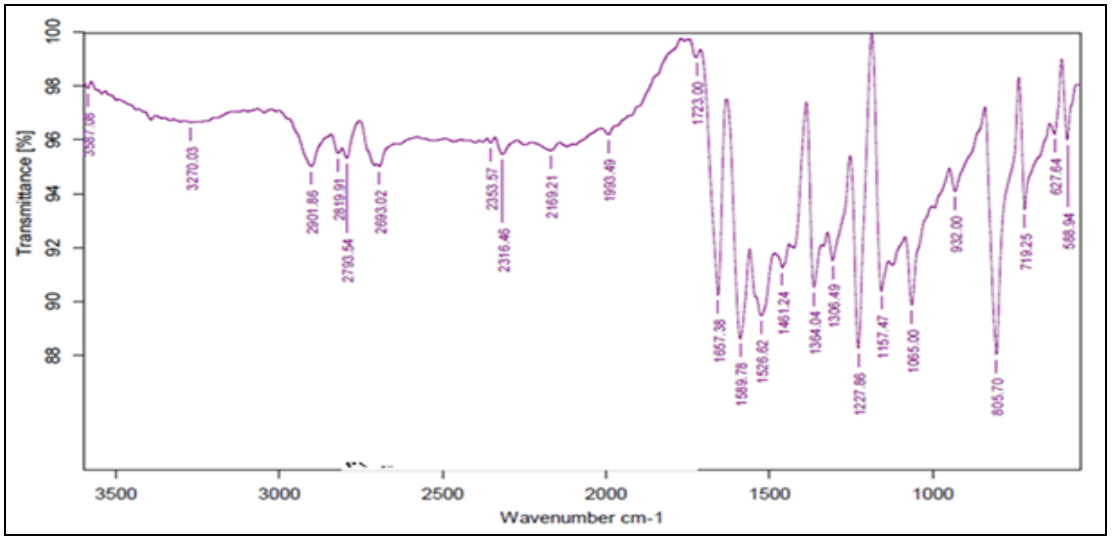

FIG. 4: FT-IR SPECTRA OF PANTOPRAZOLE WITH EXCIPIENTS

Calibration Curves:

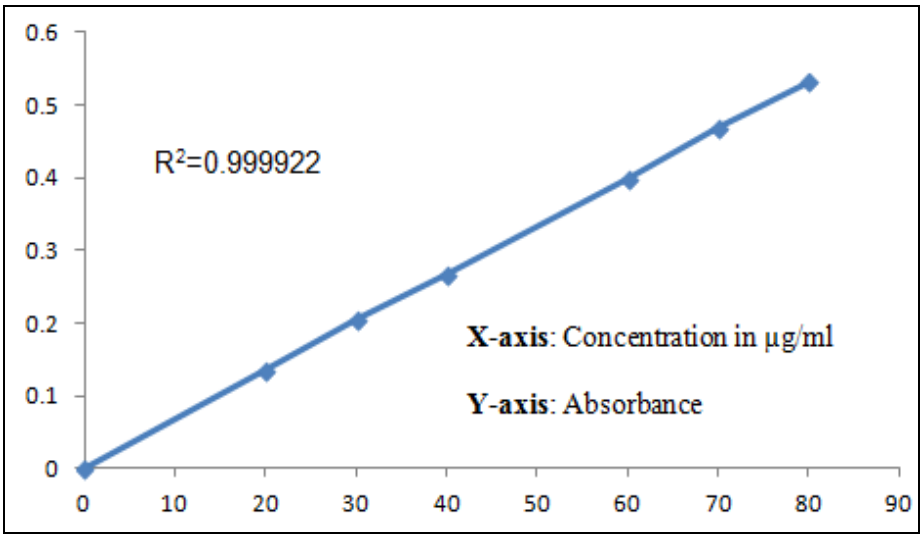

FIG. 5: CALIBRATION CURVE OF NAPROXEN IN pH 7.4 PHOSPHATE BUFFER

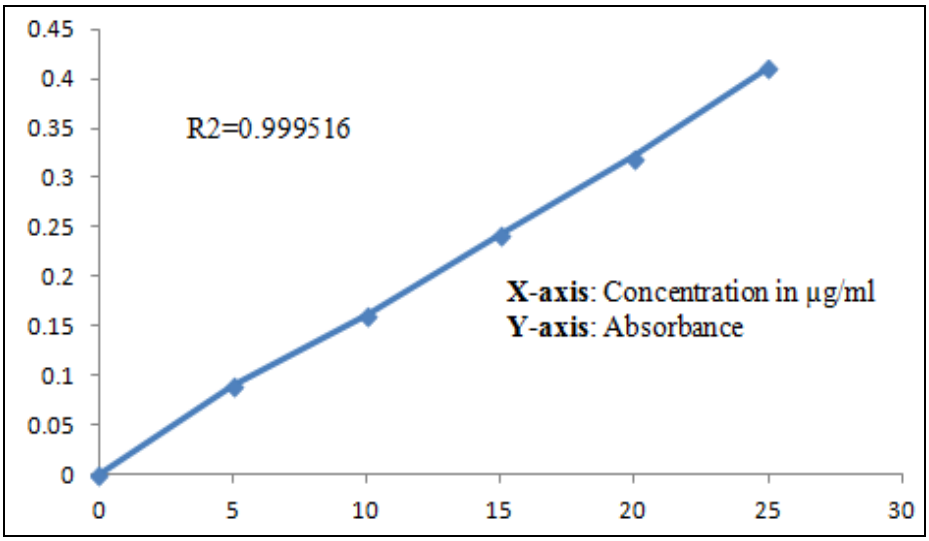

FIG. 6: CALIBRATION CURVE OF PANTOPRAZOLE IN 0.1N HCl

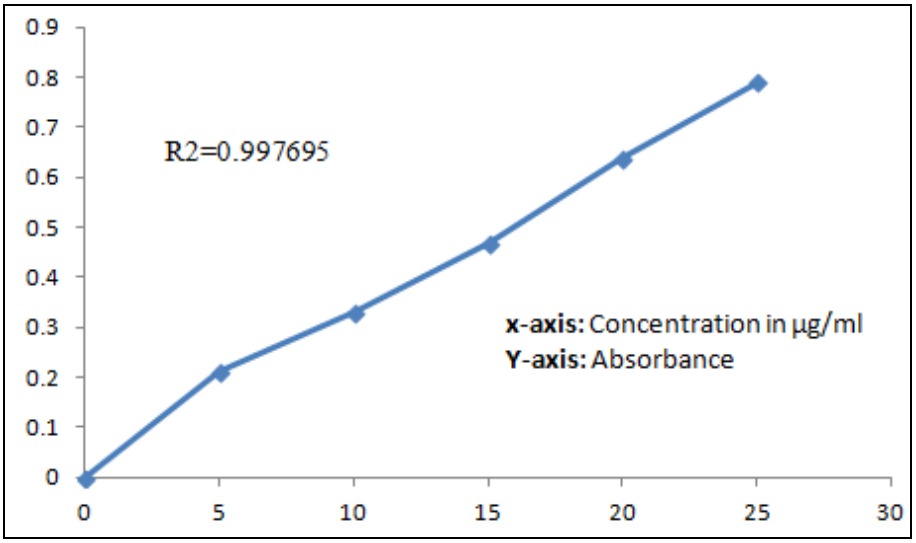

FIG. 7: CALIBRATION CURVE OF PANTOPRAZOLE IN pH 7.4 PHOSPHATE BUFFER

Preformulation Properties: The Pre-granulation and precompression flow properties such as Bulk density, Tapped density, Angle of Repose, Carr's index and Hausner's ratio values of all the five formulations (F_1 - F_5) are shown in the **Tables 6** and **7**.

TABLE 6: FLOW PROPERTIES OF POWDERS OF FORMULATIONS D_1 - D_5

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of Repose (°)	Compressibility index %	Hausner's ratio
D_1	0.55	0.63	27.8	12.7	1.14
D_2	0.39	046	23.5	15.2	1.18
D_3	0.59	0.67	22.07	11.9	1.13
D_4	0.59	0.68	24.2	13.2	1.15
D_5	0.37	0.44	25.05	15.9	1.19

TABLE 7: PRE-COMPRESSION PROPERTIES OF GRANULES OF FORMULATION D_1 - D_5

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of Repose (°)	Compressibility index %	Hausner's ratio
D_1	0.77	1.07	32.11	26.75	1.31
D_2	0.69	1.66	33.87	26.45	1.35
D_3	0.78	1.07	34.45	26.87	1.33
D_4	0.77	1.07	33.7	26.67	1.38
D_5	0.78	1.07	33.8	26.67	1.36

Evaluation of Multi-layered tablets: The tablets were visually observed and free from defects such as lamination, chipping, and capping. The prepared tablets passed all the in-process tests. The values of Weight variation, Hardness, Friability of all the six multi-layered formulations are shown in **Table 8, 9**.

TABLE 8: POST COMPRESSION PARAMETERS OF FORMULATIONS F_1 – F_5

S. no	Weight variation (mg)	Average thickness	Hardness (kg/cm3)	Friability (%)
F_1	624 ± 1.5	6.84± 0.02	3.5 ± 0.07	0.31 ± 0.09
F_2	628 ± 1.3	6.91± 0.03	4.3 ± 0.03	0.42 ± 0.03
F_3	628 ± 1.7	6.90± 0.02	3.6 ± 0.02	0.26 ± 0.08
F_4	633 ± 1.5	6.76± 0.01	3.8 ± 0.04	0.28 ± 0.06
F_5	624 ± 1.4	6.85± 0.02	4.5 ± 0.07	0.45 ± 0.04

TABLE 9: POST COMPRESSION PARAMETERS OF FORMULATIONS D_1 – D_5

S. no	Weight variation(mg)	Average thickness	Hardness (kg/cm^3)	Friability (%)
D_1	550 ± 1.5	6.14± 0.02	3.3 ± 0.03	0.25±0.07
D_2	549 ± 1.3	6.11± 0.03	4.6 ± 0.02	0.32±0.08
D_3	550 ± 1.7	6.09± 0.02	3.8 ± 0.04	0.35±0.03
D_4	549 ± 1.5	6.16± 0.015	4.2 ± 0.07	0.45±0.05
D_5	551 ± 1.4	6.15± 0.022	4.2 ± 0.04	0.25±0.02

The drug content of both Naproxen and Pantoprazole in multilayered tablets was found to be 96.5% and 103.2% respectively.

Release kinetics: The data suggested that the release kinetics of the drugs Naproxen and Pantoprazole follows first order drug release, as the values of regression coefficient obtained were highest for first order drug release profiles (R^2=0.998141).

***In vitro* Drug Release Profile:**

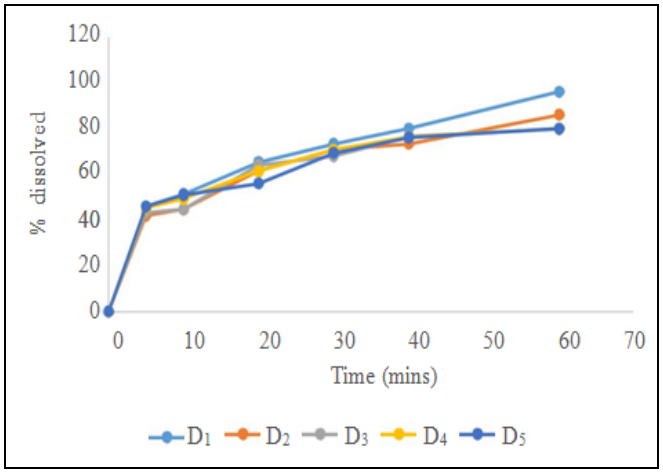

FIG. 8: DISSOLUTION OF NAPROXEN CORE TABLETS IN 0.1N HCl (D_1-D_5)

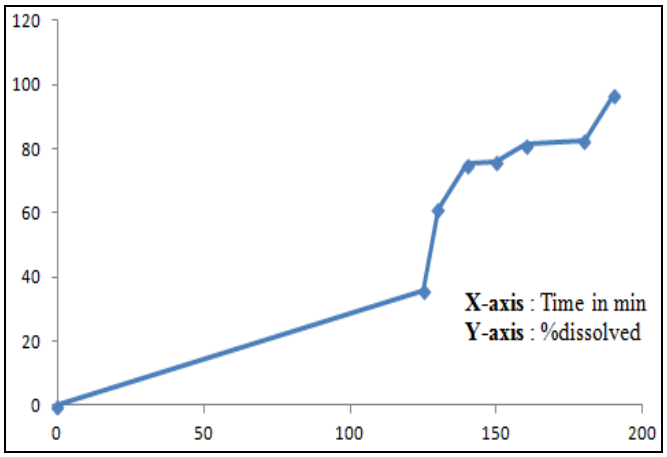

FIG. 9: DISSOLUTION OF NAPROXEN FROM ENTERIC COATED TABLET

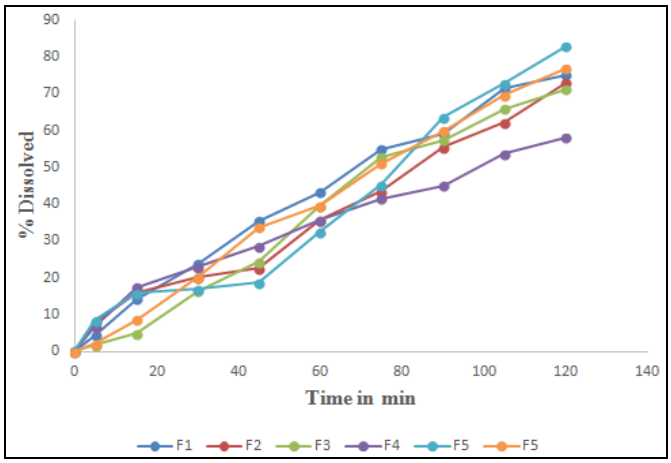

FIG. 10: DISSOLUTION OF PANTOPRAZOLE FROM MULTI-LAYERED TABLETS

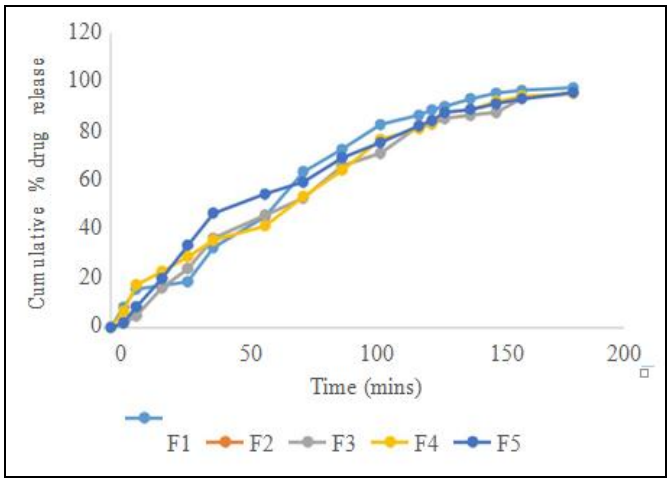

FIG. 11: DISSOLUTION OF NAPROXEN FROM MULTI - LAYERED TABLETS

SUMMARY: Calibration curves were plotted for Naproxen and Pantoprazole in both the acidic and basic media (0.1 N HCl and 7.4 pH phosphate buffer). Five formulations D_1 - D_5 were prepared for Naproxen core tablets. The drug & excipients powders showed average to poor flow properties. Hence, granulation was performed. The granules showed improved flow properties. The optimized tablets had hardness of 3.5 kg/cm^3. When dissolution was performed for formulations D_1 to D_5, the drug release studies has shown better results

for formulation D_1 (96%). So D_1 was considered as optimized core formulation, on which further coatings were performed. The five different drug layering formulations (F_1 – F_5) were coated over the above layered tablets individually using three different alkalizing agents.

As the stability of Pantoprazole was a function of pH; and it rapidly degrades in acid media, we have added the alkalinizing agents into the formulation to create an alkaline environment of the enteric coating formulation. The formulations (F_1 – F_5) were subjected to dissolution studies in 0.1 N HCl and 7.4 pH phosphate buffer as per the specifications.

The formulation containing F1 Pantoprazole drug layer has shown good result with 97.49 % of Pantoprazole release and 98.9 % of Naproxen release. The drug content of both Naproxen and Pantoprazole in multi-layered tablets (optimized formulation D_1) was found to be 96.5% and 103.2% respectively. The data from the curve fitting analysis of the drugs Naproxen and Pantoprazole in the optimized formulation D_1 showed that there is zero order drug release, as the values of regression coefficient obtained were highest for zero order drug release profiles.

CONCLUSION: More than 50 million adults have Doctor-diagnosed Arthritis. Arthritis and other non-traumatic joint disorders are among the five most costly conditions among adults 18 and older. NSAIDs, which are the most common drugs suggested for Arthritis poses risk of stomach ulceration. To overcome this, a proton pump inhibitor is generally prescribed along, which finally lead to an increase in the cost of treatment. A combination product of desired drugs can both reduce the treatment cost and improve the patient compliance. In the present study, an attempt is made to formulate a combination product of Naproxen, a widely used NSAIDs, and Pantoprazole, a proton pump inhibitor that is capable of reducing gastric acid secretion, as a multi-layered tablet. The prepared tablets contain a Naproxen enteric coated core and Pantoprazole coated around this. The results proved that the prepared drug product releases both the drugs at desired sites and with acceptable rates of release.

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CONFLICT OF INTEREST: No conflicts of interest.

REFERENCES:

1. Goldstein J L, Hochberg M C, Fort J G, Zhang Y, Hwang C, Sostek M, :Clinical trial: the incidence of NSAID-associated endoscopic Gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone. Aliment Pharmacol Ther 2010; 32: 401–413.
2. Approval of Vimovo www.accessdata.fda.gov/drugsatfda_docs/label/2014/022511s017lbl.pdf
3. Arthritis, Peptic Ulcer. www.healthline.com
4. Arthritis. www.arthritis.org
5. Arthritis, Peptic ulcer, Naproxen, Pantoprazole. www.wikipedia.com
6. Drug Profile of Naproxen http://www.drugbank.ca/drugs/DB00788
7. Lachman, Herbert A Liberman: The theory and practice of Industrial Pharmacy. Special Indian Edition 2009.
8. CVS Subrahmanyam: Textbook of Physical Pharmaceutics. Vallabh Prakashan, Second Edition 2010.
9. Patrick J. Sinko: Martin's Physical Pharmacy and Pharmaceutical Sciences. Lippincott Williams & Wilkins, Fifth Edition; 337 – 432, 533 – 583.
10. Hina Kouser Shaikh, Kshirsagar RV, Patil SG: Mathematical models for drug release characterisation: A review. World Journal of Pharmacy and Pharmaceutical Sciences, 2015; 4(4): 324-338.
11. Indian Pharmacopoeia, Vol. 3, 2014, 2305 – 2309, 2426 – 2428.
12. Drug Profile of Pantoprazole. http://toxnet.nlm.nih.gov/cgibin/sis/search/r?dbs+hsdb:@term+@rn+@rel+102625-70-7
13. Anne-Marie Schjerning Olsen, Jesper Lindhardsen, Gunnar H Gislason, Patricia McGettigan, Mark A Hlatky, Emil Fosbøl, Lars Køber, Christian Torp-Pedersen, Morten Lamberts: Impact of proton pump inhibitor treatment on gastrointestinal bleeding associated with non-steroidal anti-inflammatory drug use among post-myocardial infarction patients taking antithrombotics: nationwide study. BMJ, 2015; 351: 5096
14. Rohit Mehta, Anuj Chawla, Pooja Sharma, Pravin Pawar: Formulation and *in vitro* evaluation of Eudragit S-100 coated naproxen matrix tablets for colon-targeted drug delivery system. J Adv Pharm Technol Res, 2013; 4(1): 31–41
15. Irin Dewan, Sadiya Afrose Jahan, Mahjabeen Gazi, Joydeb Nath, Asaduzzaman Md, Maksud Al- Hasan: Design, Preparation, Evaluation, Compatability and *in-vitro* studies of Naproxen and Esomeprazole multilayer tablets: Layer by layer technology. World Journal of Pharmaceutical research, 2015; 4(6): 472-492.
16. Mukesh P Ratnaparkhi, Pravin S Pongale, Shilpa P Chaudhari: Formulation and evaluation of buffered Pantoprazole sodium tablet. International Journal of

Pharmaceutical Sciences and Research, 2013; 34, 4708-4714.
17. Patel A D, Mehta T J, Patel M R, Patel K R, Patel N M, Patel G N: Development of fast release compressed coated tablets of Rabeprazole sodium using Acid-Buffer technology. Asian J. Pharm. Res, 2011; 1(2): 53-61.
18. Newton AM, Prabakaran L, Jayaveera KN: Formulation development, optimization and study on drug release kinetics of Eudragit® L100-HPMC E15 LV mixed film-coated colon-targeted Mesalamine tablets. Asian J Pharm 2012; 6: 180-9.
19. Chien YW. "Novel Drug Delivery System". By Informa Healthcare. Second Edition; 2009; 139-140.
20. Bogan RK. Treatment options for insomnia - Pharmacodynamics of zolpidem extended release to benefit next-day performance. Postgrad Med, 2008; 120: 161-171.
21. Rathod RT, Misra D. FDC of montelukast with levocetirizine: Focus on bilayer technology. Journal of Indian Med Assoc, 2009; 107: 562-574.
22. Abdu S, Poddar SS. A flexible technology for modified release of drugs: multi layered tablets. Journal of Control Release, 2004; 97: 393-405.
23. Park JS, Shim JY, Park JS, Choi YW, Jeong SH: A novel three-layered tablet for extended release with various layer formulations and *in vitro* release profiles. Drug Dev Ind Pharm, 2011; 37: 664-672.
24. Shaikh RP, Pillay V, Choonara YE, Ndeseudo VMK, Cooppan S: A review on multi responsive membranous systems for rate-modulated drug delivery. AAPS Pharm Sci Tech, 2010; 11: 441-459.
25. Aboelwafa AA, Basalious EB: Optimization and *In vivo* pharmacokinetic study of a novel controlled release venlafaxine hydrochloride Three-Layer Tablet. AAPS Pharm Sci Tech 2010; 11: 1026-1037.
26. Namdeo B: Barrier layers in multi-layered tablets. Express Pharma, 2008.
27. Kulkarni A, Bhatia M: Development and evaluation of bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile. Iran. J Pharm Res 2009; 8:15-25.
28. Krishnaiah YSR, Karthikeyan RS, GouriSankar V, Satyanarayana V: Three-layer guar gum matrix tablet formulations for oral controlled delivery of highly soluble trimetazidine dihydrochloride. Journal of Control Release 2002; 81: 45-56.
29. Choi YW, Cui JH, Lee BJ: Formulation, release characteristics and bioavailability of novel monolithic hydroxypropyl methylcellulose matrix tablet containing acetaminophen. Journal of Control Release 2005; 108: 351-361.
30. Gautam CS, Saha L: Fixed dose drug combinations (FDCs): rational or irrational: a view point. Br J Clin Pharmacol 2008; 65: 795-796.
31. Vogeleer, Van Den Mooter, Boeckx, Jurgen; Happaerts, Wouter: Method for controlling a tablet press and such a press. Wipo patent wo2007132281a1, 2007.
32. Wong, Patrick S. L., Theeuwe, Felix, Eckenhoff, James B: Multi-layer Delivery System. US Patent 4874388; 1987.
33. Fanara, Domenico, Guichaux, Anthony, Berwaer, Monique, Deleers, Michel. Tablet comprising Cetrizine and Pseudoephedrine, US Patent 7014867, 2003.
34. Qiu YN. Chidambaram K: Design and evaluation of layered diffusional matrices for zero order sustained-release. Journal of Control. Release 1998; 51: 123-130.
35. Vyas SP, Khar RK: Controlled drug delivery. Concept and advances, 1st edition, Vallabh prakashan, Delhi, 2002; 267-347.
36. Lachman Leon, Lieberman Herbert A: Compression coated and layer tablets. In: Pharmaceutical Dosage Forms: Tablets. 2nd Edition, Marcel Dekker, Inc. New York, 2002; 1: 247-84.
37. J. L. Goldstein , M. C. Hochberg, J. G. Fort, Y. Zhang, C. Hwang, M. Sostek: Clinical trial: the incidence of NSAID-associated endoscopic Gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone. Aliment Pharmacol Ther 2010; 32: 401–413.
38. Anne-Marie Schjerning Olsen, Jesper Lindhardsen, Gunnar H Gislason, Patricia McGettigan, Mark A Hlatky, Emil Fosbøl, Lars Køber, Christian Torp-Pedersen, Morten Lamberts: Impact of proton pump inhibitor treatment on gastrointestinal bleeding associated with non-steroidal anti-inflammatory drug use among post-myocardial infarction patients taking antithrombotics: nationwide study. BMJ 2015; 351:h5096.
39. Rohit Mehta, Anuj Chawla, Pooja Sharma, Pravin Pawar: Formulation and in vitro evaluation of Eudragit S-100 coated naproxen matrix tablets for colon-targeted drug delivery system. J Adv Pharm Technol Res. 2013; 4(1): 31–41.
40. Irin Dewan, SadiyaAfrose Jahan, Mahjabeen Gazi, Joydeb Nath, Md. Asaduzzaman, Maksud Al- Hasan: Design, Preparation, Evaluation, Compatability and *in-vitro* studies of Naproxen and Esomeprazole multilayer tablets: Layer by layer technology. World Journal of Pharmaceutical research, 2015; 4(6): 472-492.
41. Mukesh P. Ratnaparkhi, Pravin S. Pongale, Shilpa P. Chaudhari: Formulation and evaluation of buffered Pantoprazole sodium tablet. International Journal of Pharmaceutical Sciences and Research, 2013; 34: 4708-4714.
42. A.D. Patel, T.J. Mehta, M.R. Patel, K.R. Patel, N.M. Patel, G.N. Patel: Development of fast release compressed coated tablets of Rabeprazole sodium using Acid-Buffer technology. Asian J. Pharm. Res. 2011; 1(2): 53-61.
43. Newton AM, Prabakaran L, Jayaveera KN: Formulation development, optimization and study on drug release kinetics of Eudragit® L100-HPMC E15 LV mixed film-coated colon-targeted Mesalamine tablets. Asian J Pharm 2012; 6:180-9.
44. Drug Profile of Naproxen http://toxnet.nlm.nih.gov/cgibin/sis/search/r?dbs+hsdb:@term+@rn+@rel+22204-53-1
45. Drug Profile of Naproxen, Pantoprazole https://pubchem.ncbi.nlm.nih.gov/
46. Drug Profile of Pantoprazole http://www.drugbank.ca/drugs/DB00213
47. Amreen Sultana and R. Balaji Reddy: Formulation and evaluation of floating bilayered tablets of Naproxen and Sumatriptan. World Journal of Pharmaceutical Research, 2015; 4(8): 2953-3008.
48. Shailendra Singh Bisht, Himanshu Chaurasia, Sugandha Varshney, Reena, Deepti Kotiyal: Formulation and evaluation of fast dissolving tablets of Sumatriptan succinate. International Journal of Pharmaceutical Sciences and Research, 2013; 4(5): 1912-1917.
49. Sudarshan Singh, Savaliya Dharmesh, Shah D. Suresh, Bothara B. Sunil: Development and *in vivo* bioavailability evaluation of Sumatriptan succinate Buccal tablets. International journal of pharmaceutical sciences and nanotechnology, 2014; 7(2): 2477-2486.
50. Rapolu Bharath Kumar, T. Vedavathi: Formulation and evaluation of Sumatriptan succinate oral disintegrating tablets and comparison of disintegrating property between

superdisintegrants and simple disintegrant. The pharma innovation, 2012; 1 (9): 73-92.
51. The Indian pharmacopeia, Edn 6, Vol. 3, Indian pharmacopeia commission, Ghaziabad, 2010; 559-560.
52. Hina Kouser Shaikh, R.V. Kshirsagar, S.G. Patil: Mathematical models for drug release characterisation: A review. World Journal of Pharmacy and Pharmaceutical Sciences, 2015; 4; 324-33.

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