



Original Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF MUCOADHESIVE TABLETS OF NORFLOXACIN CONTAINING NATURAL POLYMER

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Abstract

The present investigation deals with development and evaluation of mucoadhesive gastroretentive tablet of Norfloxacin using natural polymer from Tamarind seed polysaccharide. Natural polymers have been used widely in the sustained release of a variety of drugs to enhance their release patterns. The hypothesis behind this work is to increase the bioavailability of drug by gastro retentive approach. Different formulations (F1 to F12) have been prepared by wet granulation method. Preformulation studies such as melting point, U.V. scanning, solubility studies have been done. Drug polymer compatibility studies were done using FT-IR. Micromeretic studies such as bulk density, tapped density, carr's index, hausner ratio and angle of repose were performed. Prepared tablets were further evaluated for mucoadhesive strength, swelling index, hardness, weight variation, friability, thickness has also been evaluated. The *in-vitro* drug release studies has been done or 8hrs by using USP-II apparatus with 0.1 N HCl. Different kinetic models were applied to study the release pattern of drug from the tablet. Based on the results of different studies formulation F10 was selected as best formulation. All the parameters were found within the acceptance limit and the formulated tablet shows extended release for 8 hrs.

Keywords: Norfloxacin, Mucoadhesion, Gastroretention, Tamarind Seed Polysaccharide.

Introduction

The last two decades mucoadhesion has become of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining a formulation in intimate contact with the absorption site (e.g. buccal cavity) as mucosal membranes. (1) Mucoadhesive drug delivery systems have so far not reached their full potential in oral drug delivery, because the adhesion of drug delivery systems in the GI tract is insufficient to provide a prolonged residence time of delivery systems in the stomach or small intestine. (2) Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. (3) Mucoadhesion and bioadhesion involves two materials in which at least one is biological in nature, held together for an extended period of time by interfacial forces. Alternately it is defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. Bioadhesion involves adhesion of the polymer with the biological membrane while mucoadhesion involves adhesion of the polymer with the mucus membrane. Adhesion as a process is simply defined as the "fixing" of two surfaces to one another. (4) Gastroretentive systems can remain in the gastric region for several hours and hence can significantly prolong the gastric residence time of drugs. Prolong gastric retention improves bioavailability, reduces drug wastage, and improves solubility for the drugs that are less soluble in the high pH environment. (5)

MATERIAL AND METHOD

Materials

The drug Norfloxacin was purchased from Yarrowchem India Ltd, Mumbai, Tamarind was collected from the local market; all the excipients used in the experiment are of analytical grade and are obtained from the commercial suppliers.

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Methods

Polymer Extraction Process

The seeds of *Tamarindus indica* were washed thoroughly with water to remove the adhering materials. Then, the reddish testa of the seeds was removed by heating seeds in sand in the ratio of 1:4 (Seed: Sand). The testa was removed. The seeds were crushed lightly. The crushed seeds of *Tamarindus indica* were soaked in water separately for 24 h and then boiled for 1 h and kept aside for 2 h for the release of mucilage into water. The soaked seeds were taken and squeezed in a muslin bag to remove marc from the filtrate. Then, equal quantity of acetone was added to precipitate the mucilage. The mucilage was separated. The separated mucilage was dried at temperature 50°C, powdered and passed through sieve number 80. The dried mucilage was powdered and stored in airtight container at room temperature. (6)

Various Preformulation parameters

Melting point determination

An open end capillary tube was taken and one end is closed by fusion and the drug powder was filled into it. Then, the capillary was placed in silicon oil bath in a digital melting apparatus (model no.1013A, Perfit India) and the temperature at which the pure drug powder starts melting was noted as the melting point.

Identification tests for Tamarind Seed Polysaccharide:

Molisch's test

To the test solution add few drops of alcoholic – naphthol, then add few drops of concentrated sulphuric acid through sides of the test tube, purple to violet colour appears at the junction.

Barfoed's test

One ml of test solution is heated with 1 ml of Barfoed's reagent on water bath, if red cupric oxide is formed, monosaccharide is present. Disaccharide on prolonged heating (about 10 minutes) may also cause reduction, owing to partial hydrolysis to monosaccharides.

Test for pentoses

To the test solution add equal volume of hydrochloric acid containing with small amount of phloroglucinol and heat, red colour is produced. (7)

Bulk Density

Apparent bulk density (gm/ml) is determined by pouring bulk powder into a graduated cylinder and measuring the volume and weight. (8)

Bulk density was calculated by the following formula

$$\text{Bulk Density, } D_b = M / V_b$$

Where, M = mass of the powder

V_b = bulk volume of the powder

Tapped Density

Tapped density is the ratio of weight of dry powder to its tapped volume. The weighed quantity of dry powder was taken in a graduated cylinder. The cylinder was placed on the tap density tester (Electro lab, model ETD-1020) and subjected to USP-II method.

Carr's Consolidation / Compressibility Index

This property is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics. It can be calculated by following formula:

$$\text{Consolidation index} = \frac{(\text{Tapped Density} - \text{Fluff Density})}{\text{Tapped Density}} \times 100$$

Hausner Ratio

It was determined by using the Following formula-

$$\text{Hausner Ratio} = \frac{\text{Tapped bulk density}}{\text{Loose bulk density}}$$

Angle of repose

Flow properties of powder was determined by the angle of repose technique. Angle of repose was determined by the fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to its axis of symmetry was fixed at a given height (h) above the graph paper placed on a flat horizontal surface. The gum powder was carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. The radius (r) of the base of the pile was determined and the tangent angle of repose was calculated by following equation

$$\tan \theta = h/r$$

$$h = \text{Height of the pile} \ \& \ r = \text{radius of the pile}$$

Percentage yield

$$\text{Percentage Yield} = \frac{\text{Practical Yield}}{\text{Theoretical yield}} \times 100$$

Weight variation test

Weighed 20 tablets selected at random and calculated the averageweight. Then percentage deviation from the average was calculated. (9)

Thickness

Thickness and diameter of the tablets was measured using calibrated dial calipers by picking three tablets randomly from all the batches. Three tablets of each formulation were picked randomly and dimensions determined. It is expressed in mm and standard deviation was also calculated. Thickness was measured using a calibrated screw gauge. Three tablets of each formulation were picked randomly and thickness was measured individually. (10)

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of core tablets was determined using a hardness tester. It is expressed in kg/cm². Three tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated.

Friability test

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A pre weighed tablet was placed in the friabilator . Friabilator consists of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the

friabalator for at least 4 minutes. (11) At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{Friability} = \text{loss in weight} / \text{Initial weight} \times 100$$

Swelling Studies

The tablets of each formulation were weighed individually (designated as W1) and placed separately in petri dishes containing water. At regular intervals (1,2,4,8,10,12 hr) the tablets were removed from the petri dishes and excess water was removed carefully by using filter paper. (12) The swollen tablets were reweighed (W2), the swelling index of each formulation was calculated using the formula. (13)

$$\text{Swelling Index (S.I.)} = W2 - W1 / W1 \times 100$$

Drug Content Studies

Ten tablets were randomly sampled from each formulation, finely powdered and individually estimated for the drug content after suitable dilution with 0.1N HCl using UV-VIS spectrophotometer (UV- 1601, Shimadzu) at 279 nm.

Mucoadhesive Strength

The tablet was studied for Force of mucoadhesion as well as duration of mucoadhesion. (14) Detachment force measurement method was used. This is the method used to measure in-vitro mucoadhesive capacity of different polymers. It is a modified method developed by Martti Marvola to access the tendency of mucoadhesive materials. (7) In this method formulation is placed between two vials. The two vials just separated from each other. The total weight (gm) required to detach two vials was taken as a measure of mucoadhesive strength.

$$\text{Force of adhesion (N)} = \text{Mucoadhesive strength} \times 9.81 / 100$$

Drug Interaction Studies

The drug and polymer were mixed together in (1:1) ratio and kept undisturbed for 3 weeks. After 3 weeks these samples were subjected to FTIR analysis for determining the interaction between the same.

Figure No. 1

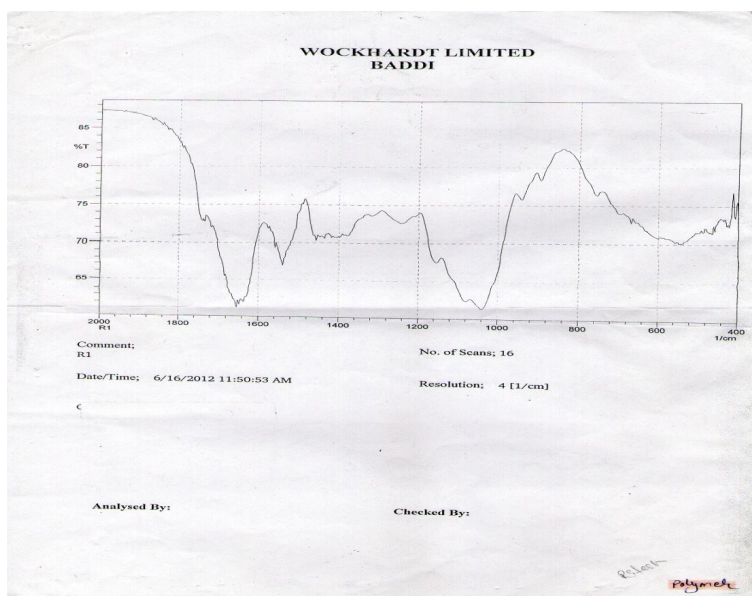


Figure No. 2

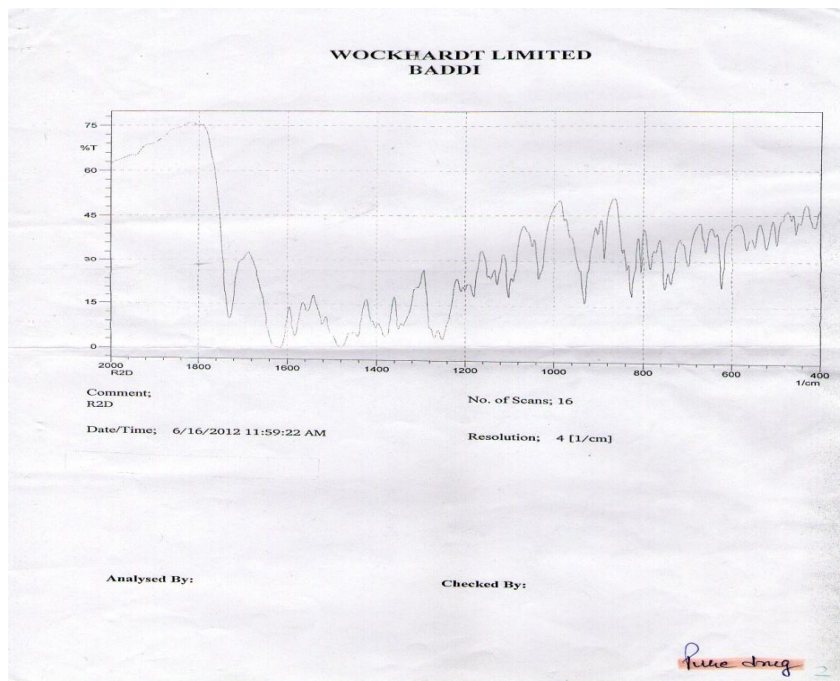
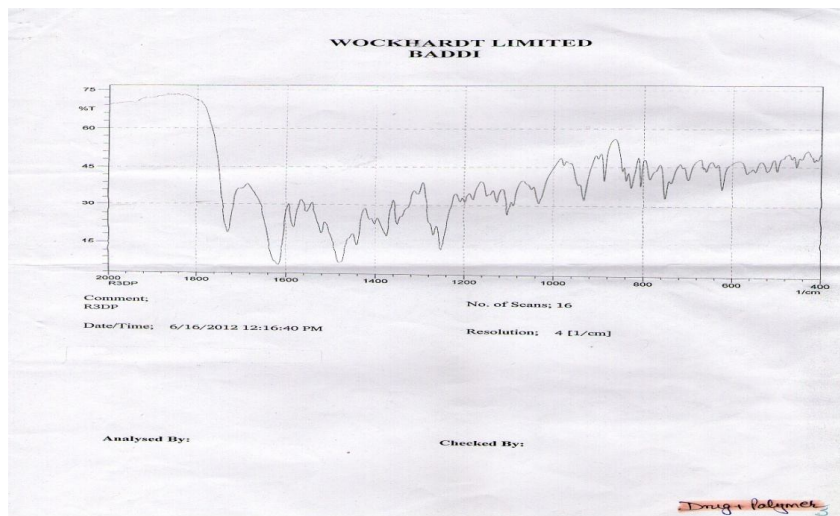


Figure No. 3



Formulation of tablet

Wet granulation method

The drug and excipients are weighed properly and mixed after passing through sieve no 40. The cohesive mass of Norfloxacin was prepared by adding required quantity of PVP K30 solution (5% w/v) to the above powder blend with thorough mixing. The wet mass was further screened out through sieve no 10 and subjected for drying in hot air oven for 40-50 minutes at a temperature of 40°C. The dried mass was finally screened out by # 16 to obtain the granules. Microcrystalline cellulose was used as a diluents in both extra as well as intra granular mode in a ratio of (80:20). Further the granules were lubricated with required quantity of talc and magnesium stearate and finally the tablets were punched using a rotary tablet punching machine.

**Table no.1 Formulation of
Norfloxacin Mucoadhesive tablet**

Formulation Code	NFC (Mg)	Polymer (TSP) (Mg)	MCC (Mg)	Mag. Stearate (Mg)	Talc (Mg)	Total weight of Tablet (Mg)
F1	400	30	207	6.5	6.5	650
F2	400	50	187	6.5	6.5	650
F3	400	70	167	6.5	6.5	650
F4	400	90	147	6.5	6.5	650
F5	400	120	117	6.5	6.5	650
F6	400	140	97	6.5	6.5	650
F7	400	160	77	6.5	6.5	650
F8	400	180	67	6.5	6.5	650
F9	400	200	37	6.5	6.5	650
F10	400	220	17	6.5	6.5	650
F11	400	240	07	6.5	6.5	660
F12	400	250	0	6.5	6.5	663

Note: NFC-Norfloxacin, TSP- Tamarind seed polysaccharide, MCC- Micro crystalline starch

RESULTS AND DISCUSSION

Melting point determination

The melting point of the obtained drug sample was found to be 220°C which is within the reported range of 221°C. It complies with the standards thus indicating the purity of the drug sample.

Polymer identification test

Table No.2 Polymer identification test

Test	Result
Molisch's Test	Positive
Barfoed's Test	Positive
Test for Pentoses	Positive

UV Scanning of Drug

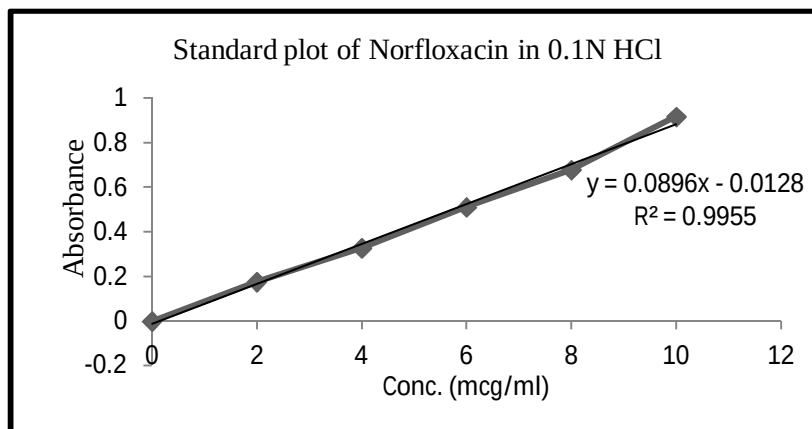
The scanning of the drug (NFC) was performed by double beam UV Spectrophotometer to determine the max of norfloxacin. It was found to be 279 nm.

Standard Plot of NFC

**Table No.3 Standard Plot of
Norfloxacin in 0.1N HCl**

S.No.	Concentration (µg/ml)	Absorbance ±S.D
0	0	0
1	2	0.177±0.002
2	4	0.328±0.001
3	6	0.511±0.002
4	8	0.679±0.002
5	10	0.917±0.015

Figure No.4



Percentage Yield

The percentage yield of the polymer was found to be 3.7%.

Table No.4 Showing Determination of Physical properties of granules

Formulation Code	Loss on Drying (%LOD)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's compressibility index	Hausner Ratio	Angle of Repose
F1	1.1	1.011±0.032	1.074±0.017	5.86±0.17	1.062±0.08	32.9±0.113
F2	1.3	1.041±0.086	1.088±0.023	4.32±0.21	1.046±0.06	30.5±0.324
F3	1.4	1.066±0.068	1.155±0.014	7.70±0.43	1.083±0.005	29.5±0.119
F4	1.6	1.026±0.053	1.091±0.032	5.95±0.66	1.063±0.02	29.7±0.192
F5	1.9	1.033±0.039	1.131±0.048	8.66±0.47	1.094±0.01	28.1±0.441
F6	2.0	1.051±0.076	1.159±0.055	9.31±0.55	1.102±0.005	26.7±0.523
F7	2.1	1.059±0.024	1.181±0.049	10.33±0.39	1.115±0.009	25.2±0.621
F8	2.3	1.062±0.043	1.231±0.073	13.72±0.76	1.159±0.006	24.5±0.765
F9	2.4	1.086±0.059	1.294±0.039	16.07±0.83	1.191±0.03	25.1±0.476
F10	2.6	1.099±0.012	1.306±0.007	15.84±0.92	1.188±0.048	22.2±0.637
F11	2.8	1.085±0.037	1.356±0.066	19.98±0.36	1.249±0.092	21.8±0.886
F12	3.0	1.095±0.028	1.396±0.042	21.56±0.19	1.274±0.03	20.3±0.221

Table No.5 Evaluation parametes of NorfloxacinTablets

Evaluation Parameters	FORMULATION CODE											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Weight	649.	650.	649.	648.	651.	650.	649.	648.	650.	649.	651.	650.0
Variation (mg)	15±0.12	07±0.18	13±0.21	23±0.08	17±0.14	11±0.26	28±0.16	02±0.31	06±0.13	12±0.18	01±0.23	4±1.24
Hardness (kg/cm ²)	5.1 ± 0.40	5.8 ± 0.56	6.2 ± 0.43	5.7 ± 0.15	6.5 ± 0.76	6.9 ± 0.27	6.1 ± 0.38	5.6 ± 0.13	6.3 ± 0.36	6.9 ± 0.15	7.3 ± 0.20	6.6 ± 0.12
Thickness (mm)	3.87 ± 0.16	3.89 ± 0.18	3.85 ± 0.32	3.88 ± 0.23	3.90 ± 0.03	3.86 ± 0.08	3.93 ± 0.16	3.91 ± 0.22	3.95 ± 0.14	3.97 ± 0.11	3.94 ± 0.27	3.96 ± 0.20
Friability (%)	0.20	0.23	0.21	0.24	0.28	0.30	0.26	0.27	0.32	0.34	0.31	0.42

Figure No.5

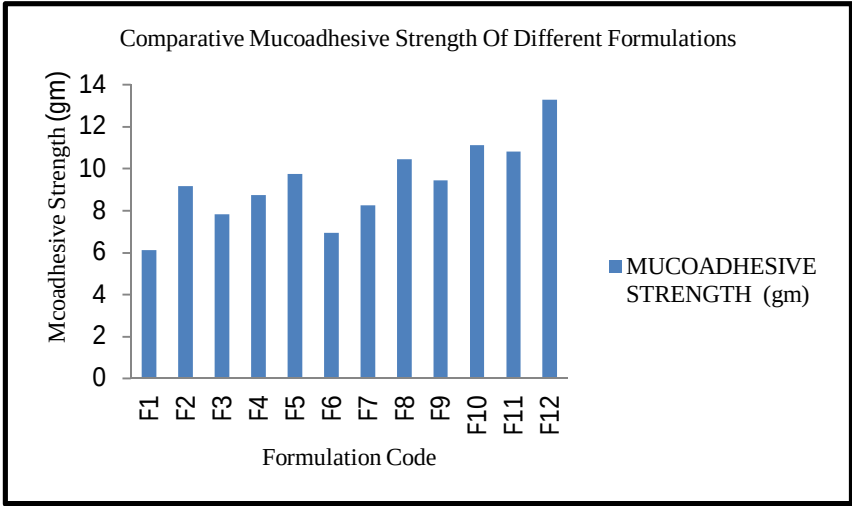
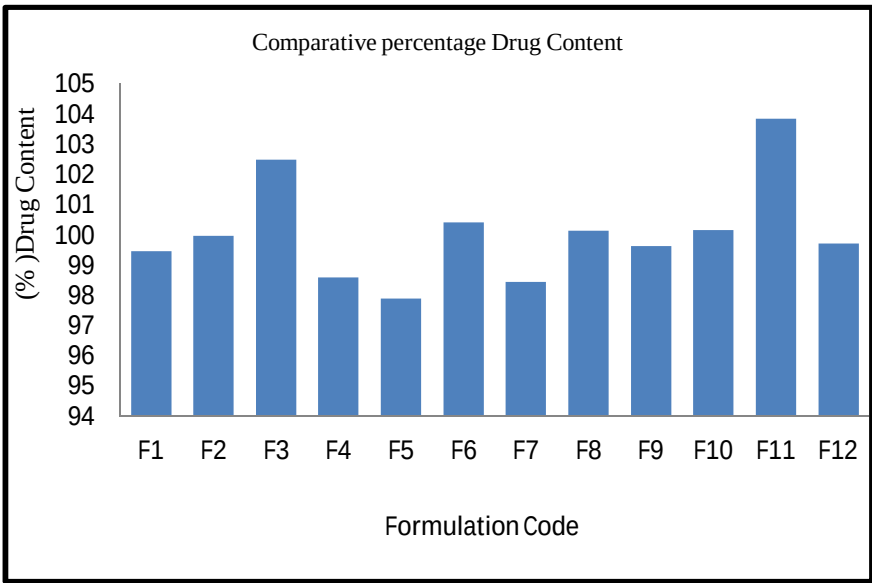


Table No.6 showing In vitro mucoadhesive strength study of prepared Norfloxacin tablets

Formulation Code	Mucoadhesive Strength (gm)(Mean±Sd)	Mucoadhesion Force (N)
F1	6.120 ± 0.547	0.600
F2	9.170 ± 0.117	0.900
F3	7.829 ± 0.753	0.767
F4	8.750 ± 0.334	0.859
F5	9.751 ± 0.816	0.957
F6	6.954 ± 0.523	0.681
F7	8.270 ± 0.149	0.812
F8	10.451 ± 0.799	1.027
F9	9.458 ± 0.334	0.928
F10	11.130 ± 0.062	1.091
F11	10.385 ± 0.145	1.019
F12	13.283 ± 0.010	1.302

Figure No.6

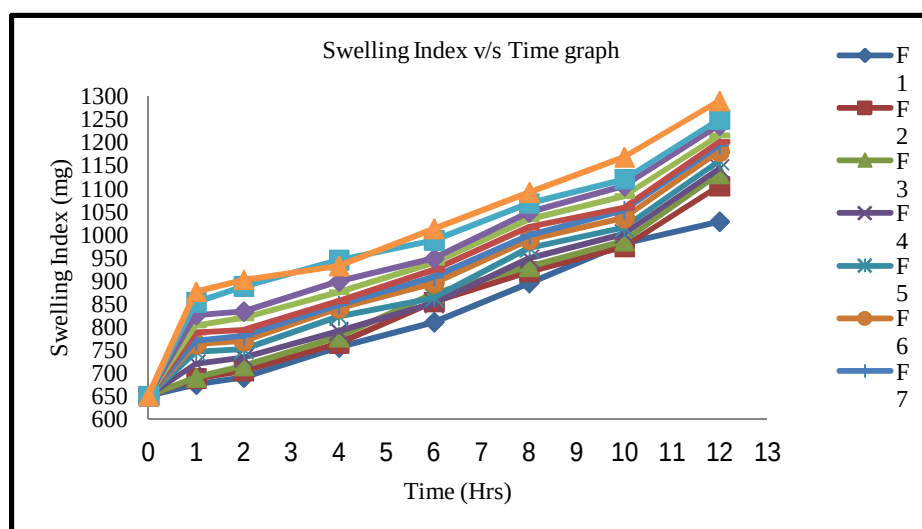


TableNo.7 showing % Drug content data

Formulation Code	Drug Content (%) (Mean $\pm$ S.D.)
F1	99.46 $\pm$ 0.40
F2	99.98 $\pm$ 0.31
F3	102.49 $\pm$ 0.36
F4	98.59 $\pm$ 0.12
F5	97.89 $\pm$ 0.45
F6	100.42 $\pm$ 0.29
F7	98.46 $\pm$ 0.36
F8	100.14 $\pm$ 0.23
F9	99.63 $\pm$ 0.27
F10	100.17 $\pm$ 0.19
F11	103.86 $\pm$ 0.03
F12	99.72 $\pm$ 0.01

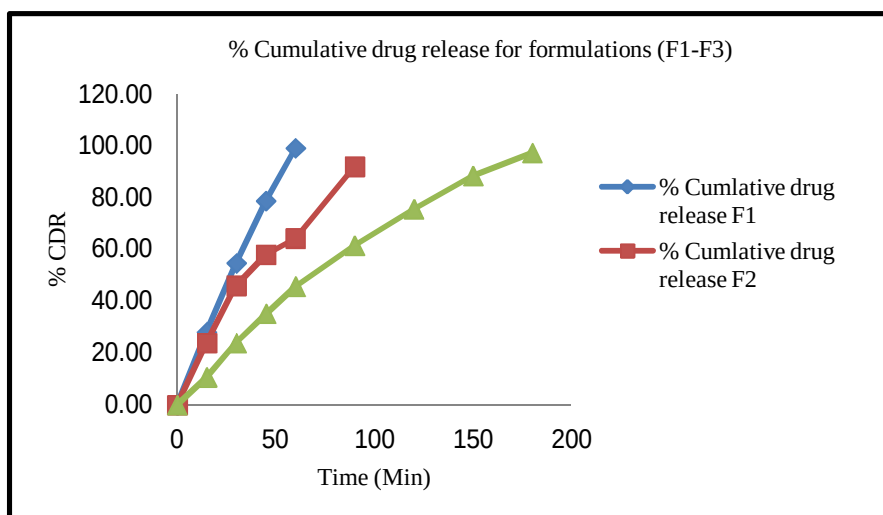
Swelling index of Norfloxacin mucoadhesive tablets

Figure No.7



Dissolution data of Norfloxacin mucoadhesive tablets (F1-F3)

Figure No.8



Dissolution data of Norfloxacin mucoadhesive tablets (F4-F12)

Figure No.9

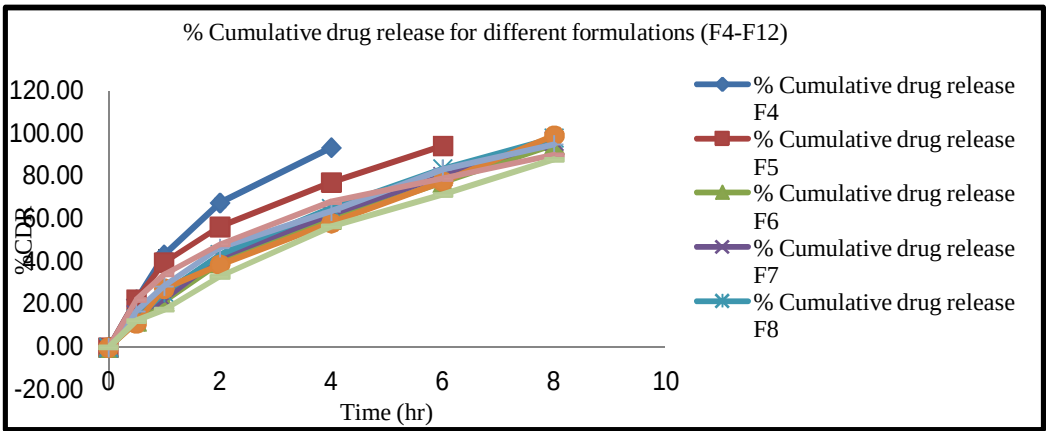


Table No.8 Showing Correlation coefficients of different mathematical models for mucoadhesive tablet of Norfloxacin

Formulation Code	Zero Order	First Order	Peppas	Higuchi	Hixson Crowell
F1	0.9946	0.7683	0.0194	0.9099	0.9131
F2	0.9325	0.9223	0.0239	0.9547	0.9814
F3	0.9574	0.8943	0.0049	0.9547	0.9778
F4	0.8628	0.9912	0.5468	0.9754	0.9984
F5	0.7931	0.9739	0.5075	0.9966	0.9893
F6	0.9407	0.9296	0.5188	0.9559	0.9817
F7	0.9234	0.9243	0.5192	0.9685	0.9825
F8	0.9042	0.8977	0.5394	0.9763	0.9781
F9	0.9411	0.7789	0.5179	0.9516	0.9189
F10	0.8666	0.9832	0.5219	0.9483	0.9919
F11	0.7382	0.9909	0.4829	0.9965	0.9816
F12	0.9538	0.9753	0.4781	0.9432	0.9948

The extraction of Tamarind Seed Polysaccharide was carried out. The drug and polymer interaction study has been carried out. Standard plot of Norfloxacin in 0.1N HCl was also performed. The slope was $y = 0.0896x - 0.0128$ and regression value was found to be $R^2=0.9955$. Identification tests (Molisch's test, Barfoed's test and Pentoses test) were performed for polymer, and result obtained from different test were positive, proving that the obtained extract of polymer contains polysaccharide. The mucoadhesive tablets of Norfloxacin containing natural polymer were carried out by wet granulation method. The tablets of different formulations (F1 to F12) were evaluated for different parameters which were discussed above. The prepared formulations (F4 to F12) achieved the goal required for ideal mucoadhesive preparations and all parameters were obtained in the acceptable limits.

CONCLUSION

From the results of melting point, scanning report, solubility studies, FTIR spectra and Differential scanning calorimeter, it can be concluded that the drug is pure with no impurities. Mucoadhesive preparations have been used widely in the sustained release of a variety of drugs to enhance their release patterns. In this investigation, mucoadhesive tablets of Norfloxacin were prepared successfully using natural polymer (Tamarind seed polysaccharide) by wet granulation method. As a natural polymer, tamarind seed polysaccharide was used due to its good bioadhesive property and high pH tolerance. Polymer and drug ratio of the system was important to obtain sustained release patterns. The yield of polymer was low and Drug content was very high for all the formulations. The drug release rates of formulations F1, F2 and F3 were very rapid. Whereas formulations F4 to F12 shows sustained release patterns. Therefore the drug release rates from formulations were dependent on the ratio of polymer used. The present formulation study of Norfloxacin was performed in an attempt to prepare mucoadhesive tablets containing natural polymer.

CONFLICT OF INTEREST: The authors of the article donot claim any conflict of interest.

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