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DEVELOPMENT AND EVALUATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF NORFLOXACIN

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ABSTRACT

Objective: Is to develop a gastro retentive drug delivery system of Norfloxacin is to overcome the biggest problem in oral drug delivery is low and erratic drug bioavailability. **Methods:** Six formulations containing retardant material were prepared with solubilising agent in different ratios. The ability of various polymers to retain the drug when used in different concentrations was investigated. Here the presence of hydrogels forming polymers in the formulation helps them to maintain buoyancy. The release rate could be modified by varying the polymer ratio. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, buoyancy, and in vitro dissolution studies. **Result:** The in vitro drug release profiles obtained for tablets (F1) shows the maximum drug release and maintained their drug release in regular intervals up to 8 hours compared with other formulations **Conclusion:** Controlled release floating drug delivery of Norfloxacin showed sufficient release for an extended period of time. As a result, the frequent dosing and possible incomplete absorption of drug can be avoided

INTRODUCTION

Controlled drug delivery system is designed to achieve a prolonged therapeutic effect by continuously releasing the medication over an extended period of time after administration at a single dose. Norfloxacin is a flouroquinolone broad spectrum antibiotic, and is used in the treatment of urinary tract infections, prostatitis and gonorrhea. Norfloxacin is least absorbed from the lower part of the gastrointestinal tract and is better absorbed from the stomach. This drug has a repetitive dose schedule (400mg twice daily), short biological half-life (3-4hrs) and reduced bioavailability (30-40%). Thus, norfloxacin is a candidate for the development of gastro retentive drug deliverysystem. [1, 2] Six formulations were prepared by using polymers HPMC,EC, Eudragit, CMC. Starch is used as binding agent. Magnesium stearate used as a lubricant, talc as a glidant. Floating tablet can be used for the local action in the proximal GIT. Poorly soluble and unstable as well as poorly absorbable (intestine) drugs are suitable candidate for floating dosage form. These systems are retained in the stomach for prolonged time due to the floating property. Floating dosage forms have been developed to float

over GI fluids and to release the drug over a desired period of time. The exhausted system after delivering the drug isemptied from the stomach. Increased gastro intestinal time is the consequent property of floating tablets. These are designed to have lesser specific gravity than the gastric contents, there by float on the gastric fluid for extended period.

Three major requirements for FDDS formulation are;

1. It must form a cohesive gel barrier
2. It must maintain specific gravity lower than gastric contents (1.004-1.01g/cc)
3. It should release contents slowly to serve as reservoir.

Advantages of FDDS are sustained drug delivery, site specific drug delivery.

To achieve and maintain the concentration of a administered drug within the therapeutically effective range it is often necessary to take drug dosage several times and thus results in a fluctuating drug level plasma. Controlled drug delivery system has been introduced to overcome the drawback of floating drug level associated with conventional dosage forms. Controlled release refers to the use of a delivery device with the objective of releasing the drug into the patient body at a predetermined rate or at specific times or with specific release profiles. Controlled release systems provide a drug release profile independent of external environment and predominantly controlled by the design of the system. It should be emphasized that the plasma level of a drug should be maintained with in the safe margin and calculated doses of drug need to be given at different time intervals by conventional dosage forms. [4, 5]

MATERIALS: The drug Norfloxacin was purchased from Chemco, Rajasthan. Eudragit was purchased from Yarrow Chemicals, Maharashtra. Hydroxy propyl methyl cellulose(HPMC),Carboxy methyl cellulose(CMC) and Ethyl cellulose were purchased from Spectrum chemicals, Kochi, Kerala. Starch, Magnesiumstearate and Talc were purchased from Fortune chemicals, Malapuram, Kerala. Glacial aceticacid and Sodiumhydroxide were purchased from Nice Chemicals, Kottayam,Kerala.

Method: Weigh accurately the amount of norfloxacin. It was transferred to a mortar and pestle and it was powdered thoroughly. To this accurately weighed polymer is added and then mixed with starch and triturated well to develop slugs then it is passed through the sieve no. 20. Granules and fines are separated and weighed. Then the granules were compressed in a single punch machine.[13

Preparation of standard graph: 100mg of pure drug is dissolved in 100ml of water. Take 10ml of this solution and make up to 100ml. From the above solution 1ml, 2ml, 3ml, 4ml, 5ml, 6ml, 7ml, 8ml pipetted into10ml standard flask then make u to 10ml and measure the absorbance at 278nm

EVALUATION

Disintegration test

Keep one tablet each in all six tubes. A disc to each tube is placed over mesh and apparatus is switched on. The tube travels upwards and downwards. Water was maintained at $37^0C \pm 2^0C$. Time taken for all the 6 tablets to break down and pass through mesh at bottom screen is noted. The tablet passes the test if all 6 tablets break down and pass through mesh at bottom of tube and time is noted. The tablet passes the test if all the 6 tablets disintegrate within the specified time. If one or two tablets failed to disintegrate the test is repeated with another 12 tablet,

tablets passes the test if 16 out of 18 tablet disintegrate with in time.

Friability test: Weigh out 10 tablets and it is placed in Roche friabilitor and apparatus is rotated at a speed of 25rpm then the tablets are removed tested and again weight is taken. The difference in weight is calculated and weight loss should not exceed standard IP and BP limits.

Hardness test: A tablet was placed between two anvils the force was applied to the anvils and crushing strength that causes the tablet to break was recorded. Hardness is the tablet crushing strength. Monsanto and Pfizer tester are the devices that are used for hardness testing.[3,13]

Weight variation test: Take 10 tablets and take individual weight of each tablet. Then average weight of each tablet is calculated by total weight divided by 10. Once average weight is calculated compare the result with IP, BP and USP standards. [3, 13

Dissolution Studies

The 750ml of pH 4 buffer was used as a medium in each vessel. The test was performed using stirring paddles at the speed of 50rpm. Tablets from different formulation placed in different vessels containing the media and dissolutions are carried out. The dissolution media were sampled with replacing fresh at the time intervals of 1, 2,3,4,5,6,7,8 hours respectively. The dissolved amount was spetrophotometrically determined at 278nm in comparison to a standard curve of standard norfloxacin.

***In vitro* buoyancy studies:**

The in vitro buoyancy was determined by floating lag time. In this method the tablets were placed in a 250 ml beaker, containing 200 ml of 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained buoyant is determined as Total Floating Time (TFT). [13, 14]

RESULT AND DISCUSSION

Floating tablet of Norfloxacin were prepared by wet granulation method using polymers such as Eudragit, Hydroxypropyl methyl cellulose (HPMC), Ethyl Cellulose (EC), Carboxy methyl cellulose (CMC).All the formulated preparations were subjected to weight variation test, Hardness test, Friability test, Disintegration Test and dissolution test. According to hardness test conducted, the maximum value was shown by F1 (3.8Kg/cm^2) and lowest value by F4 (3.2 Kg/cm^2). The next maximum value was shown by F5.According to the weight variation test conducted the result shown by the six formulations are within the IP limits. According to the friability test conducted, the maximum loss of fine particle is shown by F6 (1.12%) and the lowest value shown by the F1(0.69%). According to the disintegration test conducted, the maximum disintegration time is shown by F1 (15minutes) and the lowest value is shown by F4(8minutes). The next maximum value was shown by F2 (12minutes). The dissolution profile shows that, the drug release was found to be influenced by the polymer in the formulation. According to the dissolution test conducted F4 shows the maximum drug release as compared with other formulations. Even though F4 shows maximum release compared with other formulation, F4 failed to maintain drug release for 8 hours. 97.5% of the drug was found to be released within 5Hours. So it failed to act as gastro retentive drug deliverysystem. Formulations F1-F3 maintained their drug release in regular intervals up to 8 hours. Formulations F4-F6 is failed to maintain their drug release for full 8 hours.

Table 1: Formulation of gastro retentive tablet

Formulations	Norfloxacin	HPMC	EC	Eudragit	CMC	Starch	Mg. Stearate	Talc
F1	400mg	50mg	100mg	100mg	-	150mg	7mg	8mg
F2	400mg	100mg	50mg		50mg	150mg	7mg	8mg
F3	400mg	100mg	-	100mg	-	150mg	7mg	8mg
F4	400mg	-	50mg	-	100mg	150mg	7mg	8mg
F5	400mg	-	-	50mg	100mg	150mg	7mg	8mg
F6	400mg	50mg	50mg	-	50mg	150mg	7mg	8mg

Table 2: Preparation of standard graph

Concentration	Absorbance
0	0
10	0.125
20	0.298
30	0.448
40	0.604
50	0.726
60	0.851
70	0.969

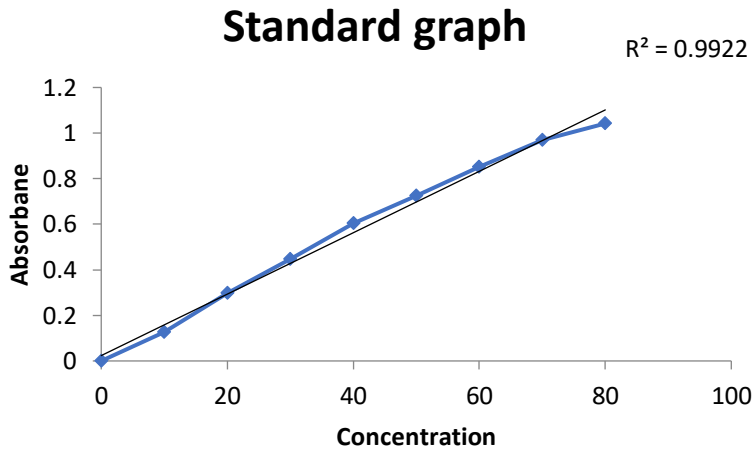

Table 2: Hardness, Friability and disintegration test

Sl/no.	Formulations	Friability (%)	Hardness (Kg/cm^2)	Disintegration Time (mins)
1	F1	0.69	3.8	15 minutes
2	F2	0.84	3.4	14 minutes
3	F3	0.81	3.5	12 minutes
4	F4	0.92	3.2	8 minutes
5	F5	1.02	3.6	10 minutes
6	F6	1.12	3.2	10 minutes

Table 3: Percentage Weight variation

Sl/no.	F1	F2	F3	F4	F5	F6
1	0.026	0.066	0.008	0.157	0.142	-1.340
2	-0.400	0.733	0.34	-0.558	1.283	-0.484
3	0.293	-0.600	-0.18	1.015	-0.142	0.912
4	-1.307	-0.206	-0.58	0.443	-1.569	-0.199
5	-0.640	0.335	-1.25	0.300	-0.713	0.085
6	0.698	-1.006	-0.45	-0.987	0.570	0.655
7	-0.375	-0.469	0.74	-1.273	0.855	1.226
8	1.095	1.130	0.34	-0.701	-0.427	-0.769
9	0.960	-0.867	-0.18	-0.014	-1.141	0.940
10	-0.565	0.672	1.14	1.588	1.141	0.798

Table 4: Percentage drug release of the formulations from F1-F6

Sl/no.	Time (Hr)	F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	10.5	17.15	15.10	25.10	30.25	9.65
3	2	15.35	28.55	25.05	30.71	45.77	18.55
4	3	17.81	37.55	35.73	51.15	52.96	25.77
5	4	37.55	60.12	48.26	72.13	65.18	35.15
6	5	48.75	67.35	51.22	80.05	72.78	47.05
7	6	62.32	85.18	78.71	88.15	83.72	51.07
8	7	78.13	92.45	85.25	92.18	88.25	72.18
9	8	94.77	92.05	90.62	97.15	90.89	78.15

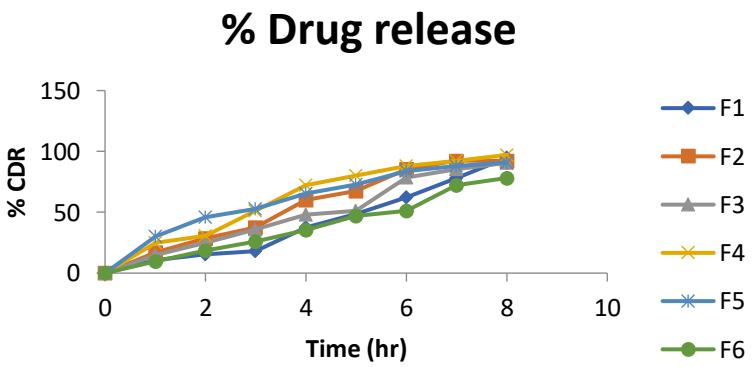

Fig 2: Percentage drug release of the formulations from F1-F6

Table 5: *In vitro* buoyancy studies

SI/NO	Formulations	Floating time (Seconds)
1	F1	120
2	F2	130
3	F3	50
4	F4	65
5	F5	55
6	F6	75

Most of these formulations (F4-F6) released their drug content within 5 hour. Formulations F1-F3 succeeded to act as gastro retentive drug delivery system because of the high concentration of polymers. The formulation F1 was selected as the best formulation because F1 succeeded to maintain drug release for 8 hours in regular time intervals. Formulation F1 was found to have maximum disintegration time (15 minutes) may because of high polymer concentration. Friability test was conducted was shown to have minimum loss of fine particles (0.69%). Hardness test of F1 ($3.8kg/cm^2$) was found to be within the limits. Formulation F1 contains Norfloxacin, HPMC, Ethyl Cellulose, Eudragit S polymer, starch, Mg-stearate, Talc as additives.

CONCLUSION

According to the study conducted formulation F1 was selected as best formulation. Formulation F1-F3 maintained their drug release in regular intervals up to 8 hours. So it was succeeded to act as gastro retentive drug delivery system. Formulation F4-F6 failed to maintain release for 8 hours. So it failed to act as a gastro retentive drug delivery system. In formulation F1-F3 polymers concentration is high. So it maintains drug release in regular time intervals up to 8 hours. Lower polymer concentration levels in F4-F6 may be the reason for their failure to act as gastro retentive drug delivery system. F1 shows satisfactory quality evaluation test like hardness test, friability test, weight variation test etc. It also shows satisfactory dissolution profile.

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