



Effect of Various Sustained Release Polymers on Naproxen Sodium Release from Control Release Tablets

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Research Article

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Abstract

Controlled release tablet of Naproxen Sodium in different formulations were included in this study. The effect of the concentration of various polymer products, fillers, and others dissolution criteria on naproxen release rate was studied. Different polymer based matrix tablets were prepared by double compression tablet machine with wet or direct compression. *In vitro* dissolution tests were performed at different intervals by USP Paddle method II. The dissolution results showed that an increased polymer concentration resulted in reduced drug release. Naproxen dissolved at specified time periods was plotted as percent release versus time (hours) curve. The drug release study was mainly performed for 8 hours because the total gastrointestinal transit time of nutrients and dosage forms in humans approximately 8 hours. We design the controlled release of Naproxen Sodium tablets satisfied with the 1st hour, 4th hour, 8th hour and 20th hour dissolution profile, respectively. To analyze the mechanism of drug release from the matrix tablet, the release data were analyzed by various equations. The data generated in this experiment indicate that various polymers have a great effect on the release rate of naproxen sodium tablet. The higher polymer level and fillers are responsible for the release rate of naproxen sodium. Excipients have negligible effect on the naproxen release.

Keywords: release polymers, Naproxen Sodium, tablets.

Introduction

Sustained Release Dosage form is design to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In case of orally administered solid (tablet/ capsule) form the release period is measured in hours and critically depends on the resistance time of the dosage form in the gastrointestinal tract (GIT)¹. The design of sustained-release delivery systems is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Obviously the biological properties of the drug are a function of its physicochemical properties².

Intranasal administration appears to be an ideal alternative to the parenterals for systemic drug delivery³. One of the major challenges in designing oral controlled release drug delivery system is to retain the dosages form in the vicinity of the absorption site for the life time of drug delivery. Several approaches have recently been developed to extend gastrointestinal transit time. It is prepared by incorporating a high level (20-75%w/w) of one or more gel forming hydrocolloids such as hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose and sodium carboxymethyl cellulose in to the formulation of and then compressing these granules into a tablet or encapsulating into capsules^{3,4}.

On contact with gastric fluid the hydrocolloid in this intragastric floating device starts to become hydrated and forms a colloid gel barrier around its surface with thickness growing with time. This gel barrier controls the rate of solvent penetration in to device and the rate of drug release from the device⁵⁻⁶. The in-vivo performance of such delivery system was assessed by comparing the plasma profile of Diazepam following the oral administration of Valrelease[®] capsule, the hydrodynamic balanced gastrointestinal delivery system containing 15 mg Diazepam as a single dose in fasted and fed subjects, and of Valium[®] tablets in the conventional dosage form, each containing 5 mg diazepam, three times a



day at 5 hours interval. The data also suggest that the ingestion of food delays the attainment of peak plasma level of diazepam for Valrelease® Capsule⁷.

The object of the present study is to develop hydrodynamically balanced gastrointestinal delivery system using hydrophilic and hydrophobic matrix materials in tablet form. Naproxen sodium was used as model drug. Hydrophilic matrix system since their introduction is becoming an interesting industrial method to prepare controlled release dosage forms for oral administration⁸. The overall release rate of a drug from this hydrophilic matrices system is controlled by one or more of the following processes; transport of the solvent into the device, swelling of the associated matrix, diffusion through the swollen matrix and erosion of the swollen matrix⁹. Although a large number of natural and synthetic polymers, single or in combination, are tested as hydrophilic excipients. Hydroxypropyl methyl cellulose (HPMC), cellulose ether, is the excipient of choice by most formulations for hydrophilic matrix preparation most probable due to its claim as a fast gel formation to control initial release and formation of strong, viscous gel and insoluble lattices to control the drug release. In Controlled release dosage form¹⁰. Two- five percent w/w of high viscosity grade polymers are used to retard the release of water-soluble drug. Poly(vinyl acetate) is a thermoplastic polymer obtained by polymerisation of vinyl acetate using a suitable starter, without solvent or with water or 2-propanol. The vast majority of the acetate moieties are attached to non-neighbouring carbon atoms of the chain. It's application in Pharmaceutical formulation or technology is as sustained release hydrophobic formulation¹¹. The acrylic acid polymer Eudragit NE 30D were developed for pH dependent, delayed release of active ingredients from oral dosage form. It's applications in pharmaceutical formulation are as follows: enteric Coatings for solid dosage form, sustained release for solid dosage form and controlled release or timed release

properties of dry powders in a number of process. It is also used in adsorbent, anticaking agent, glidant, suspending agent, tablet disintegrant, and viscosity increasing agent¹³. Naproxen is naproxen 500mg (as the sodium salt) formulated into a sustained release tablet with an immediate release portion. This ensures a rapid initial peak with Tmax and Cmax similar to conventional dosage forms. The sustained release portion ensures that therapeutic plasma levels are maintained over a 24 hour period¹⁴⁻¹⁵. The experiment was designed in an attempt to assess the feasibility of formulating low cost hydrodynamically balanced GIDS and to optimize the level of rate controlling polymer to desirable release kinetics of the active ingredients.

Material and Methodology

Naproxen Sodium was a kind gift from Drug International Limited Bangladesh. Naproxen Sodium was manufactured by Whuann Pharmaceuticals Limited.(China). Hydroxypropyl Methyl Cellulose (Methocel Several Grades) ethers were the gift of Drug International Limited. Methocel was manufactured by ColorCon (Pvt.) Limited which was supplied by Indian Originated. Kollidon SR was supplied by BASF. Aerolac-SR 100 was manufactured by Pharmaceutical Coatings (Pvt.) Limited India. Eudragit NE30D was manufactured by Rohm GmbH, Germany. All polymer were donated by Drug international Limited. Lactose, Microcrystalline Cellulose pH 101, Magnesium Stearate, Purified Talc, Colloidal silicon Dioxide and all other reagents were kindly gifted by Drug International Limited.

Table 1: Naproxen Sodium Tablet Composition (mg)

Ingredients Name	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
Naproxen Sodium	566	566	566	566	566	566	566	566	566	566	566
MethocelK-15 CR Premium(HPMCE)	350	375	-	-	-	-	-	-	390	-	-
MethocelK-100M CR Premium	-	-	350	-	-	-	-	375	-	-	-
MethocelK-4M CR Premium	-	-	-	390	-	-	-	-	-	-	-
Kollidon SR (PVA+PVP)	-	-	-	-	350	-	180	-	-	-	180
Aerolac-SR 100 (Ethylcellulose+HPMC)	-	-	-	-	-	400	-	-	-	440	-
Eudragit NE30D	-	-	-	-	-	-	150	-	-	-	200
Kollidon VA-64	-	-	-	-	-	20	-	-	-	20	-
Polyvinyl Pyrrolidone	30	30	30	5	30	-	30	30	30	-	30
Avicel PH-101	48	48	-	-	-	-	-	-	-	-	80
Lactose	-	-	50	50	50	-	50	50	50	-	50
Mg Stearate	3	2	2	2	2	-	2	2	2	-	2
Purified Talc	2	2	2	2	2	-	2	2	2	-	2
Colloidal Silicone Dioxide (Aerosil-200)	1	1	1	1	1	-	2	1	1	-	2

formulation¹². Colloidal silicon dioxide is its small particle size and large specific surface areas give it desirable flow characteristics which are exploited to improve the flow

Dissolution: 1st Hour : Not more than 20%, 4th Hour: Between 20% to 40%, 8th Hour : Between 40% to 60%, 20th Hour: Not Less than 80%. Data Analysis



Table 2 : Average Weight, Weight Variation and Hardness (N)

Sl No	Formulation	Average Weight	Weight Variation	Hardness
1	F-01	1000.5mg	+0.15%, -0.136%	190N
2	F-02	1024.63mg	+ 0.114%, -0.169%	213N
3	F-03	1000.36mg	+0.198%, -0.277%	285N
4	F-04	1016.4mg	+0.212%, -0.232	179N
5	F-05	1000.7mg	+0.477%, -0.314%	364N
6	F-06	986.83mg	+0.226%, -0.149%	156N
7	F-07	957.01mg	+0.483%, -0.320%	220N
8	F-08	1026.5mg	+0.342%, -0.342%	275N
9	F-09	1040.8mg	+0.861%, -1.099%	218N
10	F-10	1026.45mg	+0.698%, -1.249%	152N
11	F-11	972.01mg	+0.483%, -0.320%	231N

Results and Discussion

The effect of content level of various sustained release polymer and different type of fillers are contain the formulation on the release profile of naproxen sodium is illustrated in figure-1 to figure-11.

Fig-12A illustrate In-vitro dissolution of formulation F-11 containing Eudragit NE 30D 200mg (20.57%), Lactose 50mg, (5.14%), Avicel PH 101 80mg(8.23), 30mg (3.08%) of Povidone K 30 and Kollidon SR 180mg (18.51%) and also containing lubricating agent Mg stearate 2mg, Talc 2mg and Colloidal silicon dioxide 2mg. It was found that the release rate of F-11 was similar to the reference profile but release rate of 4th hour is more and gradually release rate were slow illustrate the 8th and 20th hour. The figure 12B illustrate that the data analysis of different release rate and F-11 follows the Higuchi relationship and first order kinetics model. The curve illustrate that the log (%) release were linearity against of square root of time. Mathematically Higuchi curve shows cumulative percentage of naproxen release.

Figure-13 illustrates the release profile of F-1, F-2 & F-9. F-1, F-2 & F-9 contains 35%, 37.5% and 39.0% of Methocel K15M CR premium and same quantity of fillers and lubricants. After dissolution it was found that F-1 was more naproxen liberated in 1st, 4th, and 8th hour but 20th hour was similar to other formulation because polymer ratio is less than other F-2 and F-9 formulation. Figure-14 illustrate the release profile of F-3 & F-8. F-3 & F-8 contains 35 % & 37.5% of MethocelK100M CR premium change the filler. It was found that F-3 was more naproxen liberated in 1st and 8th hour but 20th hour was similar to other formulation. F-8 was similar to the reference release rate and more corrective than F-3. Figure-15 illustrate the release profile of F-5, F-7 & F-11. F-5 contains 35% of Kollidon SR and 4.8 % of Soluble filler Lactose. It was single preparation . F-5 was more naproxen liberated in 1st, 4th, and 8th hour but 20th hour was retard the release of naproxen to other formulation. F-7 and F-11 had not effect on filler or polymer formulation. F-7 & F-11 was a polymer independent formulation. On the other hand, F-7 & F-11 were combination

preparation with Eudragit NE 30D. It contains 4.70% of Eudragit NE-30D and 18.80% of Kollidon SR of total weight. F-11 contains 6.17% of Eudragit NE30D and 18.80% of Kollidon SR. F-7 is more naproxen liberated than F-11. Figure-16 illustrate the release profile of F-6 & F-10. Aerolac-SR-10 contains different concentration in different formulation. It was found that F-6 was more naproxen liberated in 1st, 4th, and 8th hour but 20th hour was similar to other formulation.

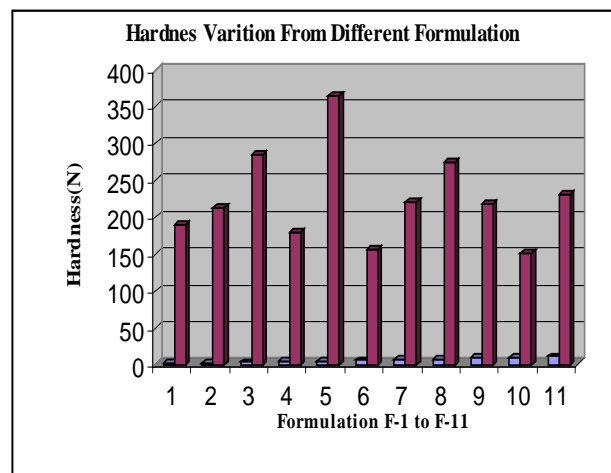


Figure: 1 Cumulative Hardness (N) in various formulations from F-1 to F-11

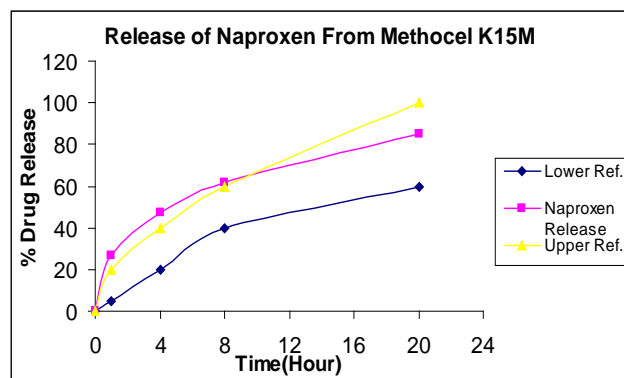


Figure: 2A Naproxen Release Profile from F-1(■) formulation and reference release.

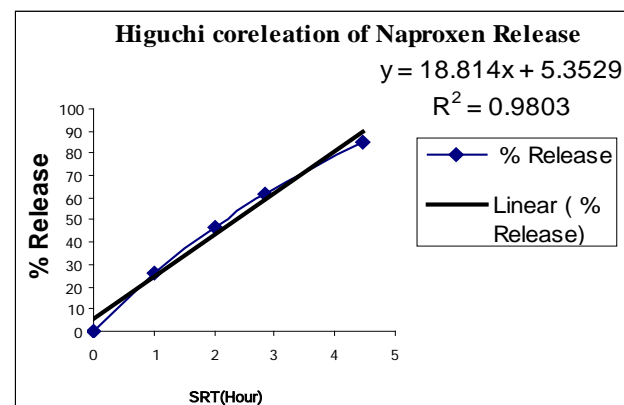


Figure-2B. Cumulative percentage of Naproxen Release on F-1

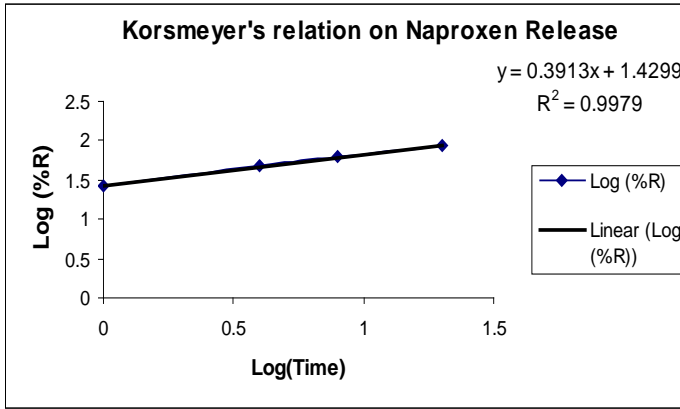


Figure-2B Log cumulative percentage of Naproxen release on F-1.

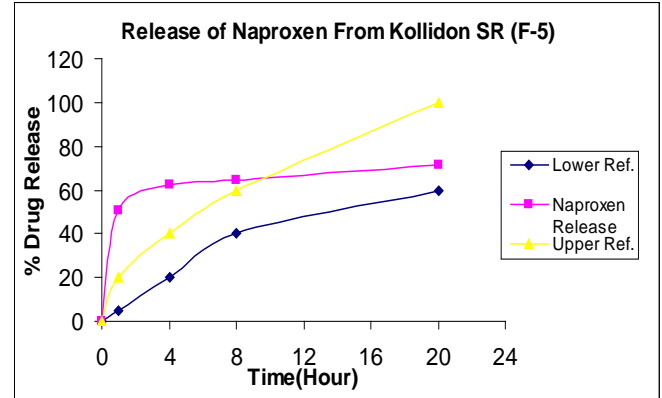


Figure-6A Naproxen Release Profile from F-5 (■) formulation and reference release

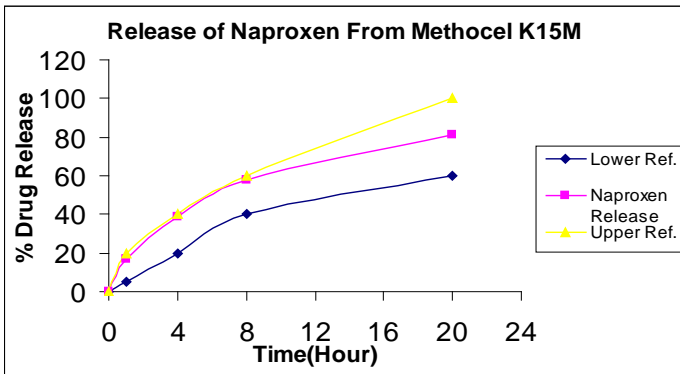


Figure-3A Naproxen Release Profile from F-2 (■) formulation and reference release.

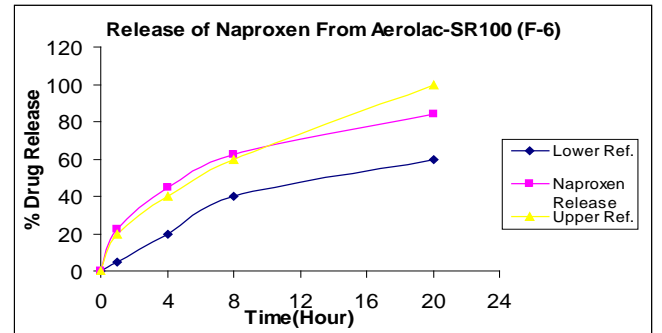


Figure-7A Naproxen Release Profile from F-6 (■) formulation and reference release.

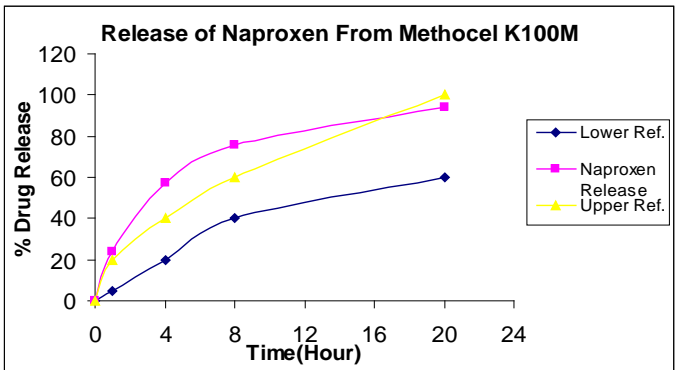


Figure-4A Naproxen Release Profile from F-3(■) formulation and reference release.

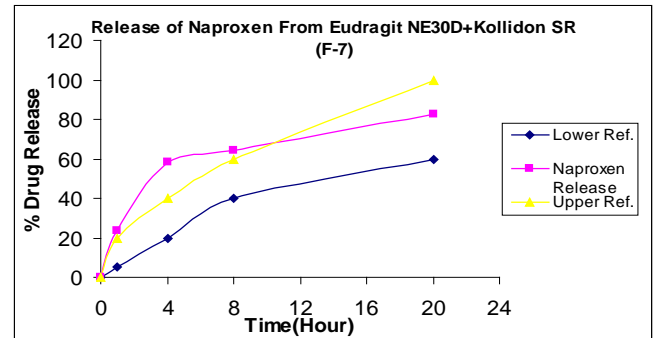


Figure-8A Naproxen Release Profile from F-7 (■) formulation and reference release.

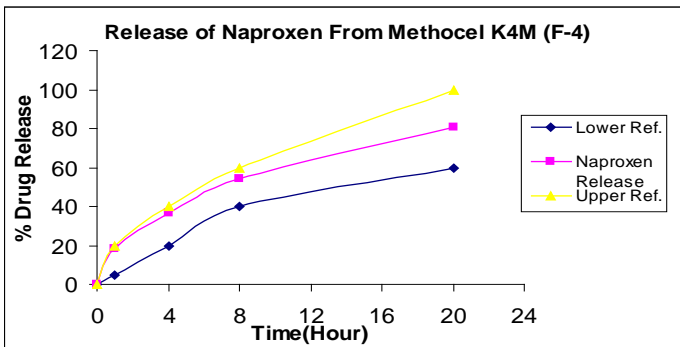


Figure-5A Naproxen Release Profile from F-4 (■) formulation and reference release

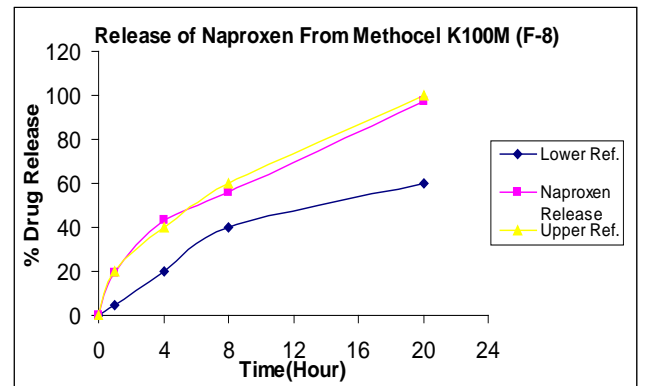


Figure-9A Naproxen Release Profile from F-8 (■) formulation and reference release

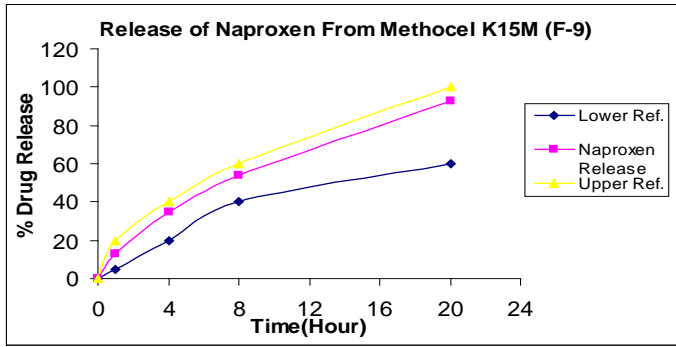


Figure-10A Naproxen Release Profile from F-9 (■) formulation and reference release.

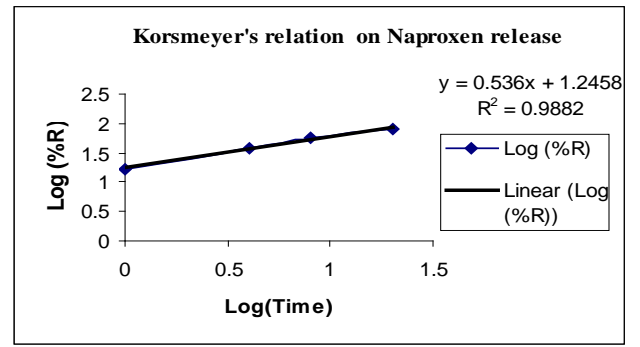


Figure-3B Log cumulative percentage of Naproxen release on F-2.

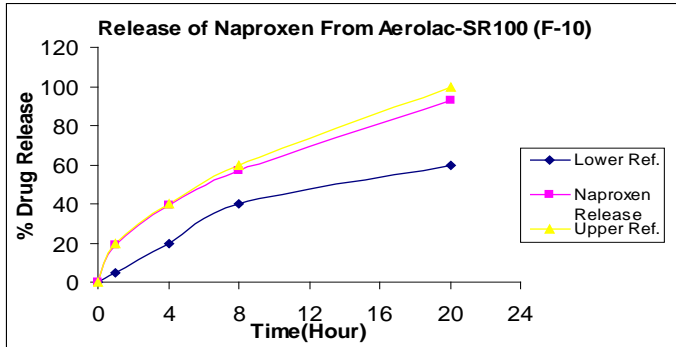


Figure-11A Naproxen Release Profile from F-10 (■) formulation and reference release.

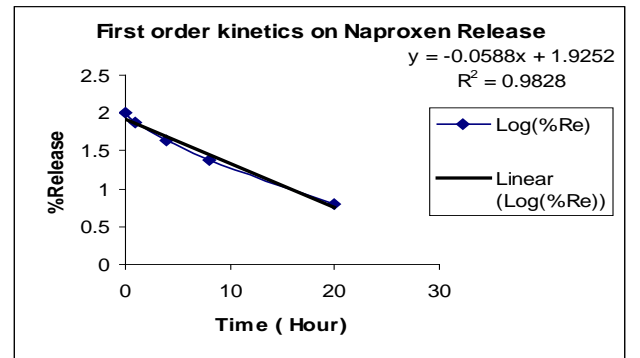


Figure-4B Log percentage of Naproxen remaining on F3

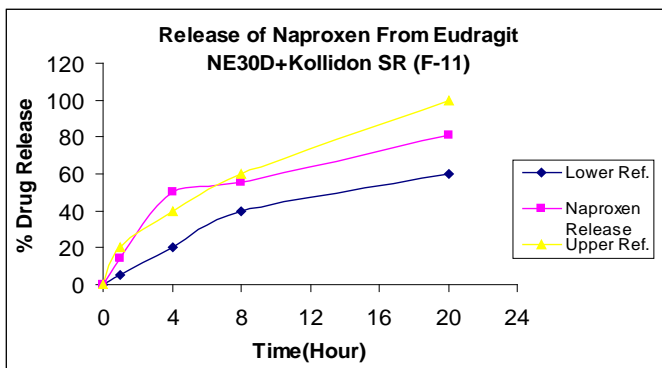


Figure-12A Naproxen Release Profile from F-11 (■) formulation and reference release

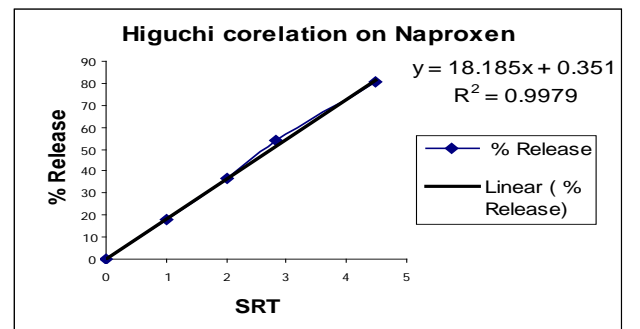


Figure-5B Cumulative percentage of Naproxen Release on F-4

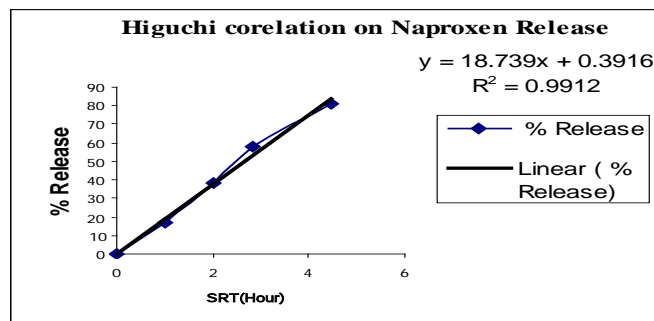


Figure-3B Cumulative percentage of Naproxen Release on F-2

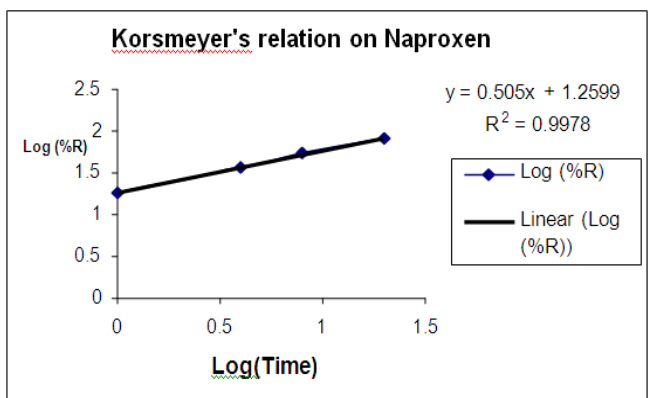


Figure-5B Log cumulative percentage of Naproxen release on F-4

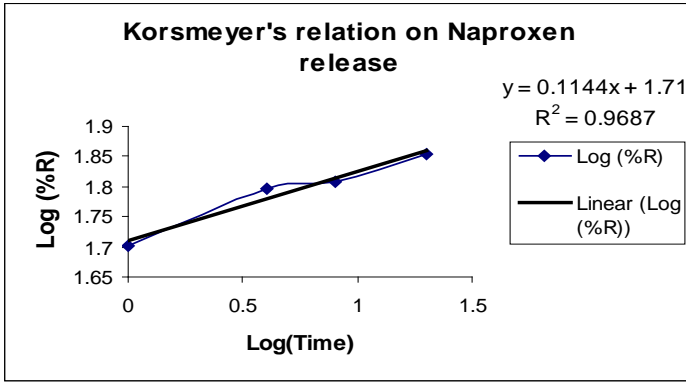


Figure-6B Log cumulative percentage of Naproxen release on F-5

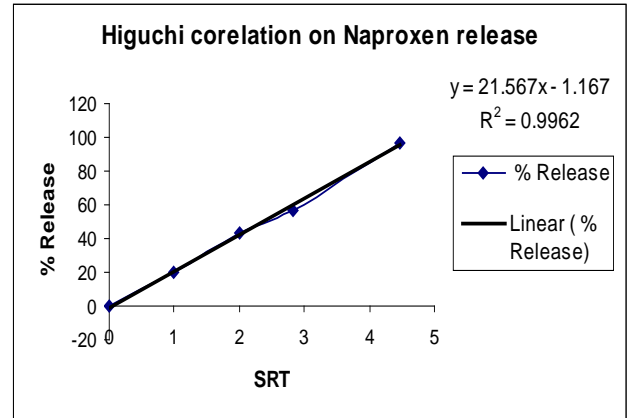


Figure-9B Cumulative percentage of Naproxen release on F-8

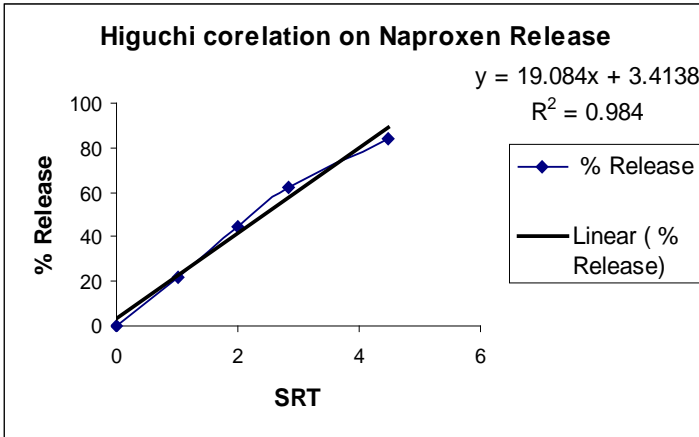


Figure-7B Cumulative percentage of Naproxen release on F-6

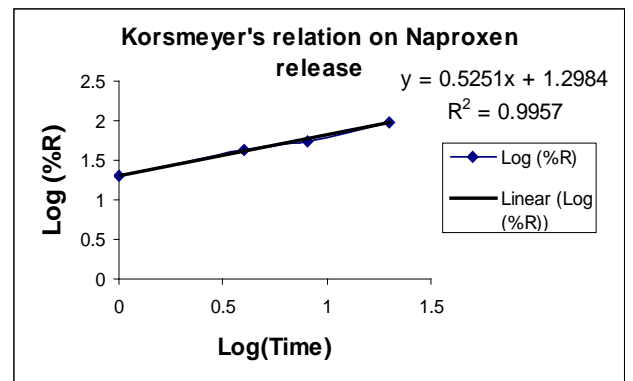


Figure-9B Log cumulative percentage of Naproxen release on F-8

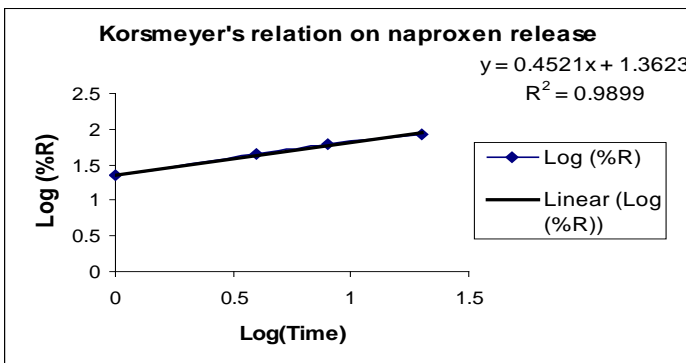


Figure-7B Log cumulative percentage of Naproxen release on F-6

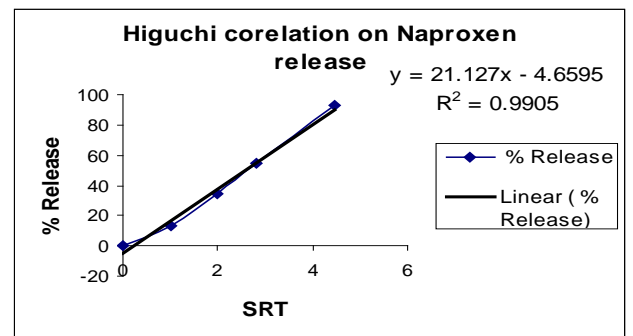


Figure-10B Cumulative percentage of Naproxen release on F-9

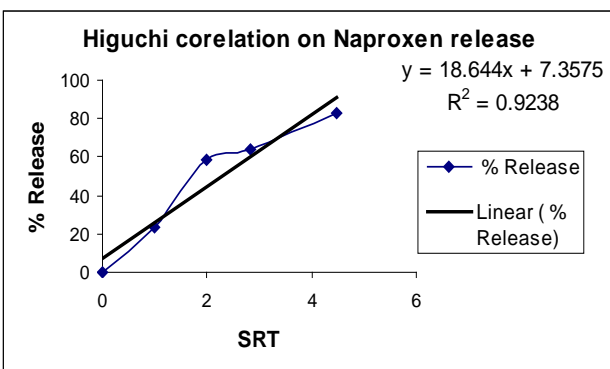


Figure-8B Cumulative percentage of Naproxen release on F-7

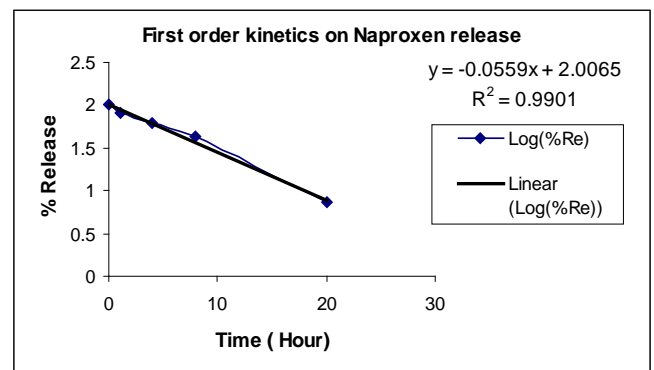


Figure-11B Log percentage of Naproxen remaining on F-10

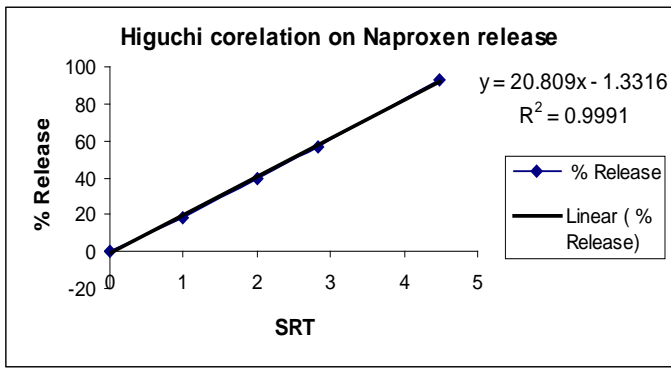


Figure-11B Cumulative percentage of Naproxen release on F-10

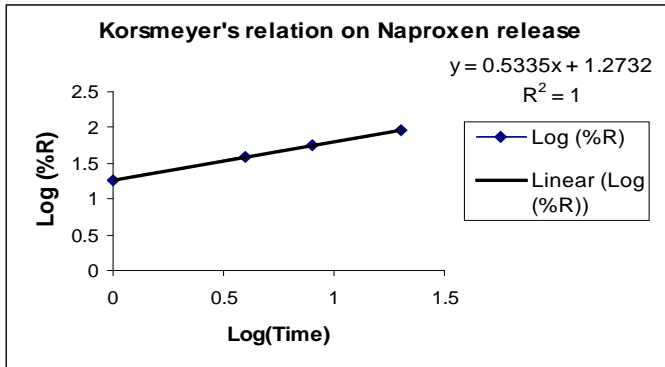


Figure-11B Log cumulative percentage of Naproxen release on F-10

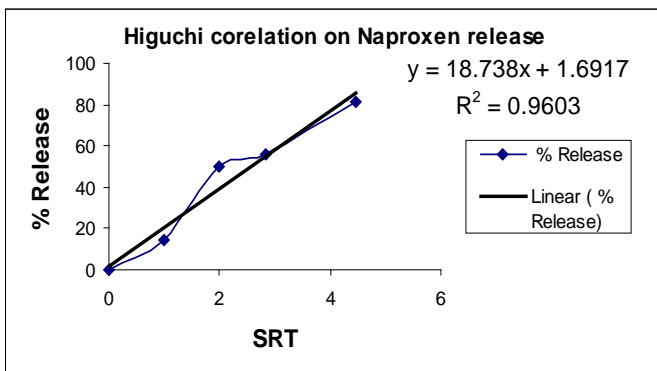


Figure-12B Cumulative percentage of Naproxen release on F-11

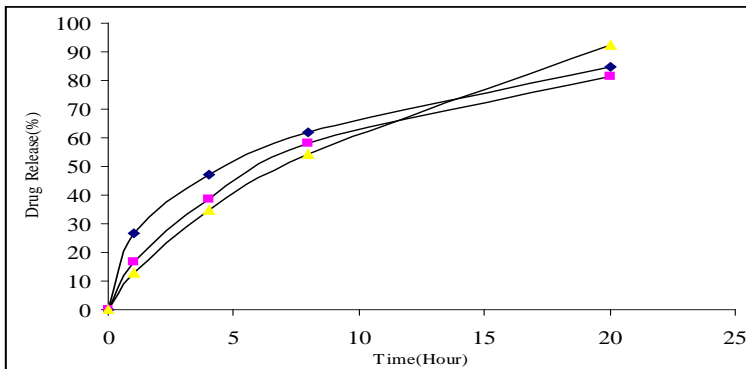


Figure: 13 Cumulative percentage of Naproxen released from formulation F-1(♦), F-2(■) & F-9(◀)

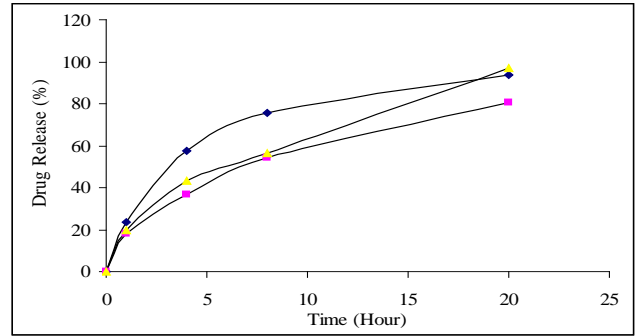


Figure: 14 Cumulative percentage of Naproxen released from formulation F-3(♦), F-4(■) & F-8(▲)

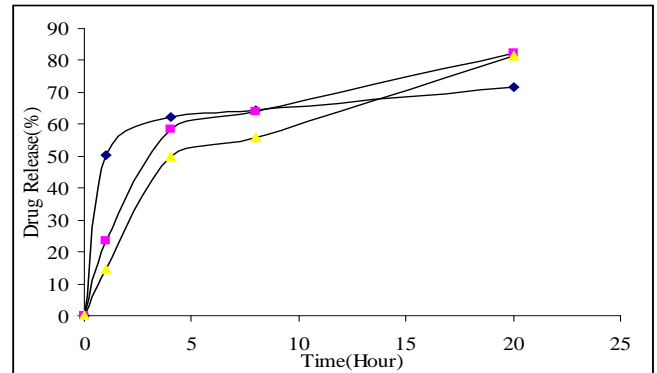


Figure: 15 Cumulative percentage of Naproxen released from formulation F-5(♦), F-7(■) & F-11(▲)

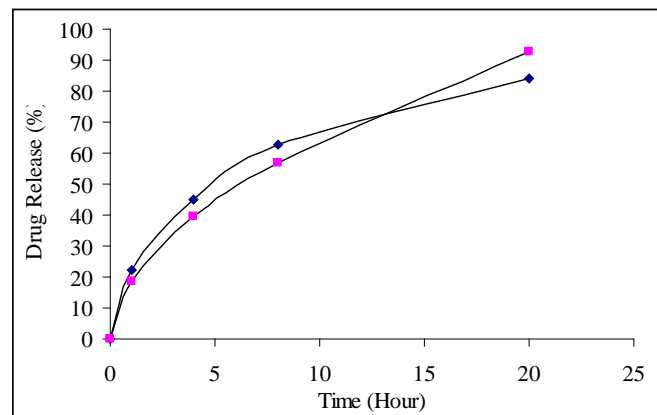


Figure: 16 Cumulative percentage of Naproxen released from formulation F-6(♦) & F-10(■).

Conclusion

Naproxen Sodium formulations generated by the modification of naproxen release rates from matrix system. The presence of soluble (Lactose, Povidone-K30, & Co-povidone) or insoluble (Microcrystalline Cellulose) fillers affect the release rate of naproxen sodium from various hydrophilic polymer. A decrease in the polymer concentration MethocelK-15M CR Premium and binding agent povidone-K30 produced an increase in naproxen release (F-1 & F-2) and follows the first order kinetics. Another way an increase MethocelK15M CR premium and lactose



ratio produced a decrease in naproxen release (F-9). Tablet containing 1:7 of Formulation F-1, 1:7.8 of Formulation F-2 and 1.8 of formulation F-9 released respectively 21.63%, 42.95%, 60.05%, 13.05%, 34.60%, 54.14% and 92.53 of naproxen over 8 hours.

Release of Naproxen, the presence of soluble fillers (Lactose and Povidone-K30) improved the naproxen release. An Constant MethocelK100M CR premium(F-3 & F4 but increase Polymer in F-8) or MethocelK4M CR premium than decrease the release rate but increase Polymer concentration than decrease the release rate at 8 hours respectively but release rate is increase after 20 hours (F-3, F-4 & F-8). For water insoluble polymer likely hydrophobic in nature matrix tablets, inclusion of soluble diluents (Lactose) change the naproxen release. Lactose and povidone-k30 dissolution may create void spaces in the insoluble polymer structure that result in increased naproxen release. An increase in the Eudragit NE30 D and Kollidon SR ratio decrease in the naproxen release. For Eudragit NE30D and Kollidon SR matrix substituting with insoluble filler Avicel PH 101(F-11) produced slow disintegration and relatively slow naproxen release (14.48% in 1st hour).

For hydrophilic polymer Aerolac-SR 100 concentration is increase than decrease the release rate of naproxen sodium. Tablets contain with highest polymer concentration than release rate is 18.75%, 39.35%, and 56.85% respectively after 8 hours (F10). However similar formulation increases the release rate after 20th hours 92.74%. The data generated in this experiment indicate that various polymer has a great effect on the release rate of naproxen sodium tablet. This higher polymer level and fillers are responsible for the release rate of naproxen sodium. Excipients have also effect on the naproxen release. So a judicious combination of excipients and technical selection of polymers can maintain the release rate of naproxen sodium tablet.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.