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Formulation and evaluation of combination porous tablet containing naproxen sodium as immediate release and sumatriptan succinate as sustained release

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ABSTRACT
Migraine is a chronic disorder and characterized by splitting headaches. A combination of sumatriptan succinate and naproxen sodium was found to be effective. Time to reach C_{max} and biological half-life of both drugs are different and hence optimum levels of both drugs cannot be maintained simultaneously in the blood when these drugs administered orally in the form of conventional tablet. Therefore the object of present study was formulation development in vitro evaluation of porous combination tablet dosage form containing Naproxen sodium as immediate release in 45min and sumatriptan succinate as sustained release to maintain optimum plasma levels of both drugs at a time and for a prolonged period of 12hrs. And here using sublimating agents camphor, and superdisintegrants like SSG for immediate release and HPMC K100M polymer to sustain the drug release.

Keywords: Naproxen Sodium, Sumatriptan Succinate, Camphor, HPMC K100M

INTRODUCTION

DRUG DELIVERY SYSTEM

Dosage forms are also referred to as "Drug Delivery Systems" or "Finished Drug Products". A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and site of release of drugs in the body. The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. Oral route of drug administration is most appealing route for delivery of drugs for various dosage forms. The tablet is one of the most preferred dosage forms, because of its ease of administration, accurate dosing and stability as compared to oral liquid dosage forms.

Tablets may be defined as solid unit pharmaceutical dosage forms containing drug substance with or without suitable excipients and prepared by either compression or molding methods[1].

Sublimation is the process of transformation directly from the solid phase to the gaseous phase without passing through an intermediate liquid phase. Sublimation is an endothermic phase transition that occurs at temperatures and pressures below a substance's triple point in its phase diagram.

At normal pressures, most chemical compounds and elements possess three different states at different temperatures. In these cases, the transition from the solid to the gaseous state requires an intermediate liquid state. Note, however, that the pressure referred to here is the partial pressure of the substance, not the total (e.g., atmospheric) pressure of the entire system. So, all solids that possess an appreciable vapor pressure at a certain temperature usually can sublime in air (e.g., water ice just below 0°C). For some substances, such as carbon and arsenical, sublimation is much easier than evaporation from the melt, because the pressure of their triple point is very high, and it is difficult to obtain them as liquids.

The aim of present study is to design and formulate combination of porous tablet containing naproxen as immediate release and sumatriptan as sustained release using sublimation technique. The main objective of this work is to overcome the physical incompatibility of sumatriptan and Naproxen, where Naproxen entraps sumatriptan and retards the release of sumatriptan.

METHODOLOGY

CALIBRATION CURVE OF NAPROXEN IN 6.8 PH BUFFER

Preparation of stock solution

Accurately weighed amount of 100 mg was transferred into a 100ml volumetric flask. Few ml of was added to dissolve the drug and volume was made up to 100 ml with 6.8 ph phosphate buffer. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'.

Preparation of working standard solution

From this stock solution 10ml was taken and diluted to 100 mL with 06.8 pH buffer which has given the solution having the concentration of 100 mcg/ml.

Preparation of serial dilutions for standard calibration curve

Necessary dilutions were made by using this second solution to give the different concentrations of naproxen sodium (2-10mcg/mL) solutions.

The absorbances of above solutions were recorded at λ_{max} (230nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

CONSTRUCTION OF STANDARD GRAPH OF SUMATRIPTAN (pH 6.8 BUFFER)

Preparation of stock solution

Accurately weighed amount of 100 mg was transferred into a 100ml volumetric flask. Few ml of water was added to dissolve the drug and volume was made up to 100 mL with pH6.8 buffer. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'.

Preparation of working standard solution

From this stock solution 10ml was taken and diluted to 100 mL with pH6.8 buffer which has given the solution having the concentration of 100 mcg/mL.

Preparation of serial dilutions for standard calibration curve

Necessary dilutions were made by using this second solution to give the different concentrations of Sumatriptan (2-10mcg/mL) solutions.

The absorbances of above solutions were recorded at λ_{max} (282nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis)

FORMULATION DEVELOPMENT

- The porous tablet was prepared by wet granulation method.
- The formulation divided into two parts intra granular ad extra granular.
- As shown in Table intra granular powder mixtures of sumatriptan, microcrystalline cellulose, polymers and binder(pvpk) were added and prepared damp mass and passed through the sieve and obtained granules were dried at hot air oven.

- The extra granular mixture of Naproxen, ccs, sublimating agent (menthol, camphor), mg sterate. The mixtures were then blended for 10 min powder blend was manually compressed using hydraulic press at a pressure of 1 ton, with a 12mm punch and die to obtain the tablet.

Table:1 composition Of Porous Combination Tablet

composition(mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F11	F12
Sumatriptan	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
HPMC K100M	55	*	82.5	*	55	*	82.5	*	96.25	96.25	82.5	82.5
EC	*	55	*	82.5	*	55	*	82.5	*	*	13.75	27.5
PVPK	22	22	22	11	22	22	22	22	22	22	22	22
MCC	11	11	11	22	11	11	11	11	11	11	11	11
Naproxen	250	250	250	250	250	250	250	250	250	250	250	250
Menthol	27.5	41.25	27.5	41.25	*	*	*	*	*	*	*	*
Camphor	*	*	*	*	27.5	41.25	27.5	41.25	41.25	41.25	41.25	41.25
MCC	93.25	79.5	65.75	52	93.25	79.5	65.75	52	38.25	24.5	38.25	24.5
CCS	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	27.5	41.25	27.5	27.5
Mg.Sterate	13.75	13.75	13.75	13.75	13.75	13.75	13.75	13.75	13.75	13.75	13.75	13.75
TOTAL	550	550	550	550	550	550	550	550	550	550	550	550

RESULTS AND DISCUSSION

The present study was carried out on the formulation and development of combination porous tablet containing naproxen sodium as immediate and sumatriptan succinate as sustained release.

PREFORMULATION STUDIES

Drug – Excipient Compatibility Study

FTIR Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

IR spectrum of physical mixture of drug with excipients revealed that there was no appreciable change in position and intensity of peak with respect to IR spectrum of pure NAPROXEN SODIUM and SUMATRIPTAN SUCCINATE analysis revealed that there was no known chemical interaction between drug and excipient

EVALUATION OF PRECOMPRESSION BLEND

All the prepared powdered blends were evaluated for Angle of repose, Bulk density, Tapped density, compressibility index, and hausner's ratio.

Angle of repose ranged from 25-30 indicates excellent flow properties.

The values of Bulk density ranged from 0.331-0.388 gm/ml and tapped density ranged from 0.381-0.446 gm/ml. the free flowing properties of powder blend were further confirmed by carr's index and Hausner's ratio.

The carr's index values and Hausner's ratio values ranged from 11.25-14.85% and 1.13-1/17 respectively, indicating all the values were within the limit as per U.S.P.

EVALUATION OF POSTCOMPRESSION BLEND

All the tablets were round in shape with no visible cracks having smooth appearance. The average weight variation of 20 tablets was remained within 1.18% this weight variation test revealed that the tablets were within the range of Pharmacopoeia limit.

All the tablets showed in the range of 3.33-3.42 mm. all the tablets showed reasonably good hardness values ranged from 7.42-7.94.

Further, to strengthen these values friability values were also considered. The percentage weight loss of formulations was less than 0.3%. This indicates that all the tablets with stand the mechanical shocks during handling.

The % drug content of all batches of tablets was determined and it was within the range of 97.5-99.9% indicating good uniformity among different formulations of the tablets. All these values of all compressed tablets were within the limits as per U.S.P.

IN VITRO DRUG RELESE STUDIES

In vitro drug release studies for the prepared tablets were conducted for a period of 12 hrs using USP type 11 dissolution test apparatus. Dissolution study of all formulations carried out using ph 6.8 phosphate buffer for 12hrs at 37± 0.5^0c with 50 rpm speed at every interval, 5ml of sample was withdrawn, after filtration appropriate dilution was done and he sample solution were analyzed at 230 nm and 282 nm for naproxen and sumatriptan succinate by uv-visible spectrophotometer.

The cumulative percentage drug released for formulations containing different polymers in different concentrations as shown in composition table. The formulation containing hpmc k100m 20% showed the drug relese 99.9 of naproxen sodium in 45 min and 99.9% sumatriptan succinate in 12hrs.

In vitro drug release kinetics for sustained release

In order to elucidate the mode and mechanism of drug release, the *in vitro* data of optimised formulation transformed and interepreted at graphical interface constructed using various kinetic model. In vitro relese data obtained for sustained relese formulation in phosphate buffer pH 6.8 was fitted into various kinetic models. The result were shown in graph the kinetics and release mechanism were estimated by the regression plots for zero order and first order, or Higuchi model and Korsemeyer- peppas model'

When R2 value of regression plots for first order and zero order were considered, it was evident that the drug relese from combination tablet followed zero order release kinetics.

Release Mechanism

The exact mechanism of drug release the was Incorporating into the Kosemeyer- peppas model and the mechanism of the drug release indicated according to the values of release exponent "n".

The release exponent values 'n' for porous tablet of sumatriptan succinate was found 1.2685. so it indicates that the formulation undergo non-Fickian diffusion(super case-11 transport) or anomalous diffusion.

In vitro drug release kinetics for immediate release

In order to elucidate the mode and mechanism of drug release, the *in vitro* data of optimised formulation transformed and interepreted graphical interface constructed using various kinetic model. In vitro relese data obtained for immediate relese formulation in phosphate buffer pH 6.8 was fitted into various kinetic models. The result were shown in graph the kinetics and release mechanism were estimated by the regression plots for zero order and first order.

When R2 value of regression plots for first order and zero order were considered, it was evident that the drug relese from combination tablet followed first order release kinetics.

CALIBRATION CURVE

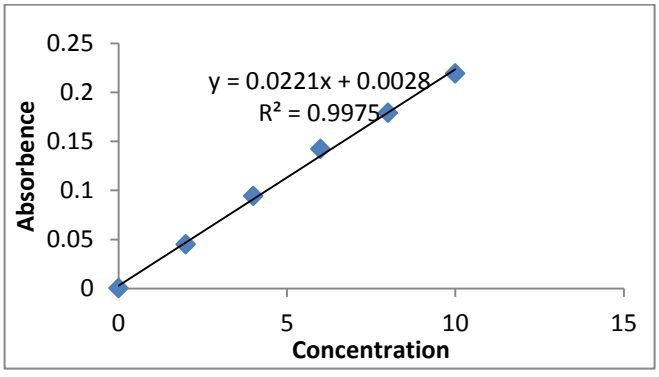

Fig:1 Standard calibration curve of Naproxen sodium in 6.8 pH phosphate buffer

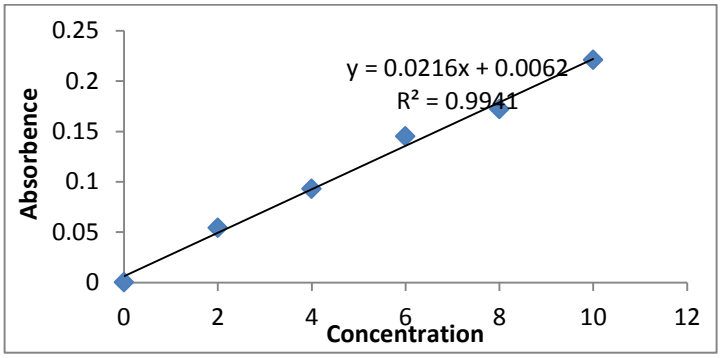

Fig:2 Standard calibration curve of Sumatriptan Succinate in 6.8 pH phosphate buffer .

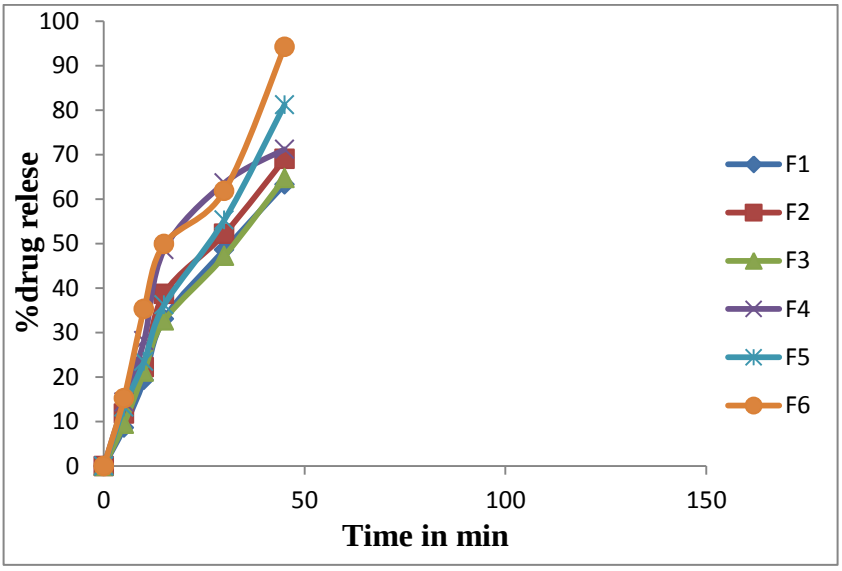

Fig: 3 Dissolution Profiles (F1-F6) For Naproxen release

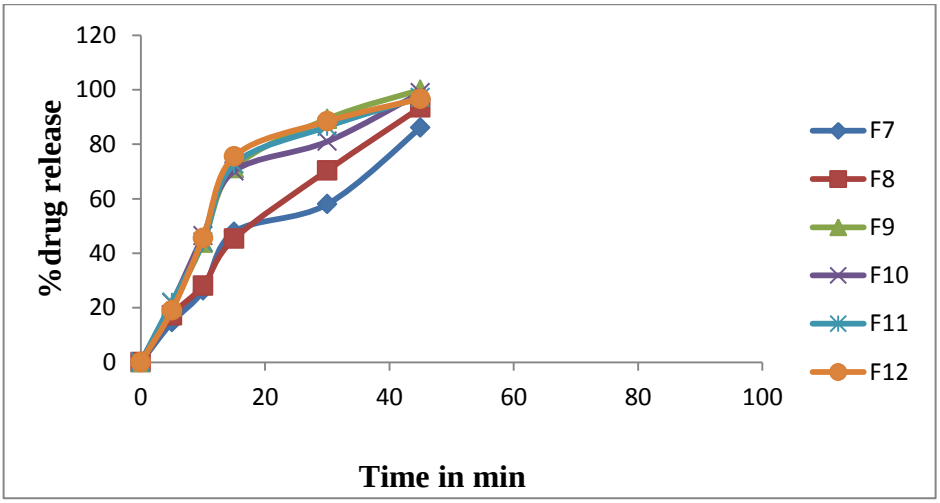

Fig:4 Dissolution Profiles (F7-F12) For Naproxen release

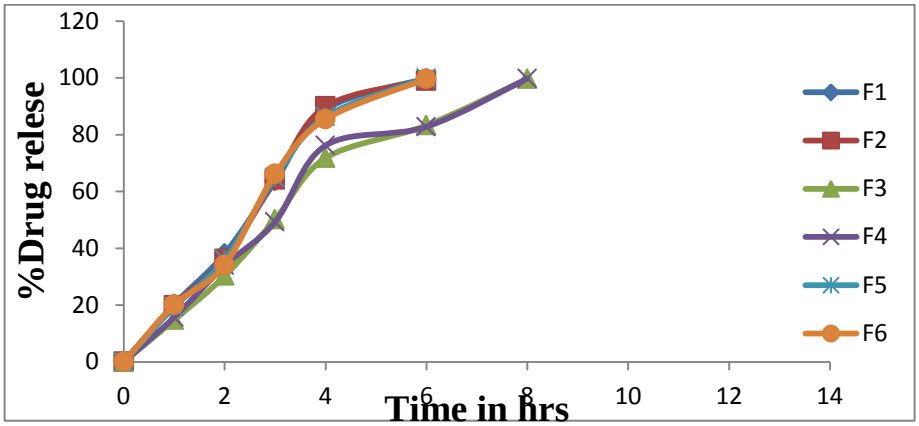

Fig: 5 Dissolution Profiles (F1-F6) For Sumatriptan release

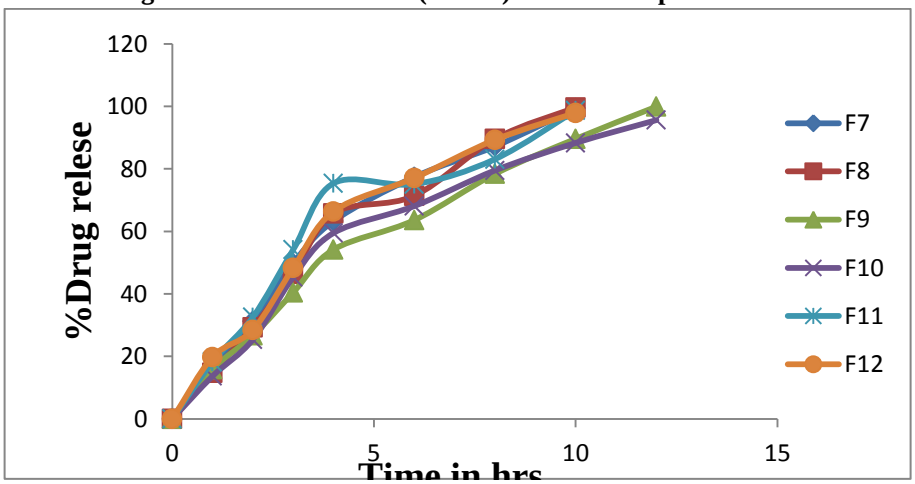

Fig:6 Dissolution Profiles (F7-F12) For Sumatriptan release

KINETICS RELEASE DATA FOR SUMATRIPTANRELESE

ZERO ORDER KINETIC GRAPHS FOR ALL FORMULATIONS F1-F12

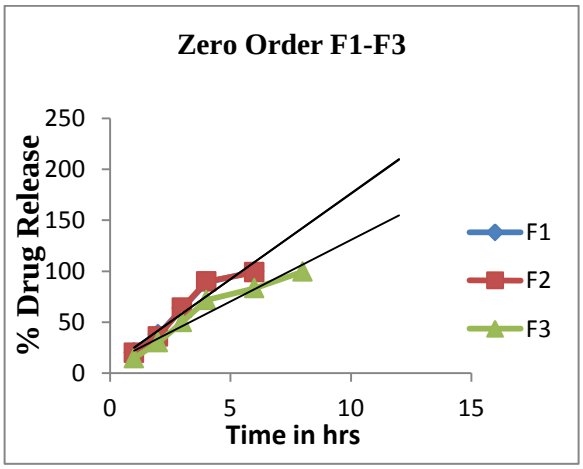

Fig: 7 Zero Order F1-F3

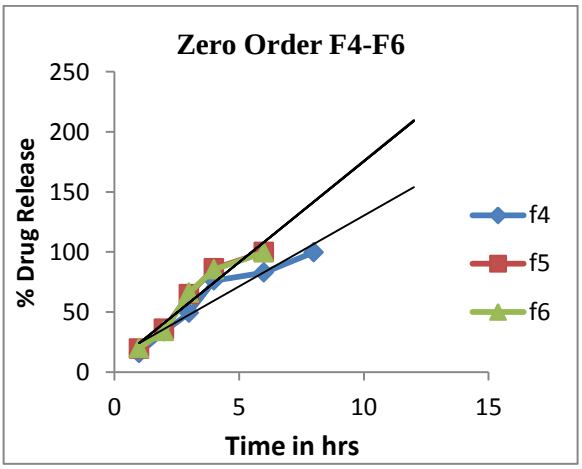

Fig: 8 Zero Order F4-F6

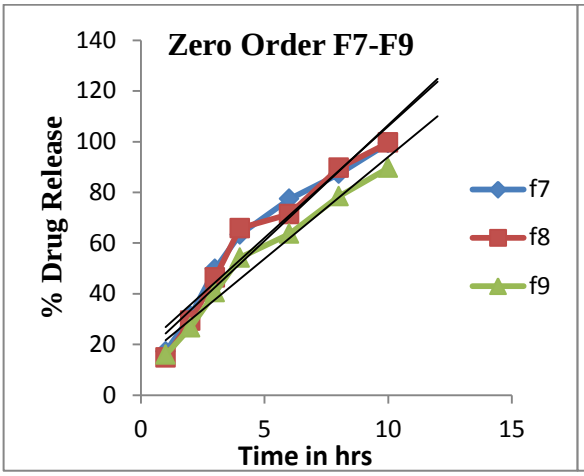

Fig: 9 Zero Order F7-F9

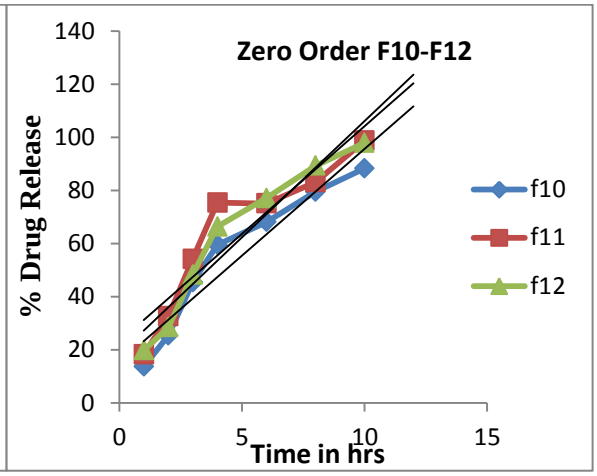

Fig: 10 Zero Order F10-F12

FIRST ORDER KINETIC GRAPHS FOR ALL FORMULATIONS F1-F12

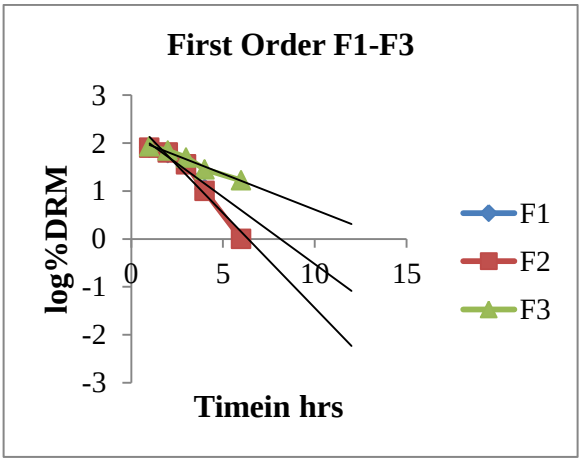

Fig: 11 First Order F1-F3

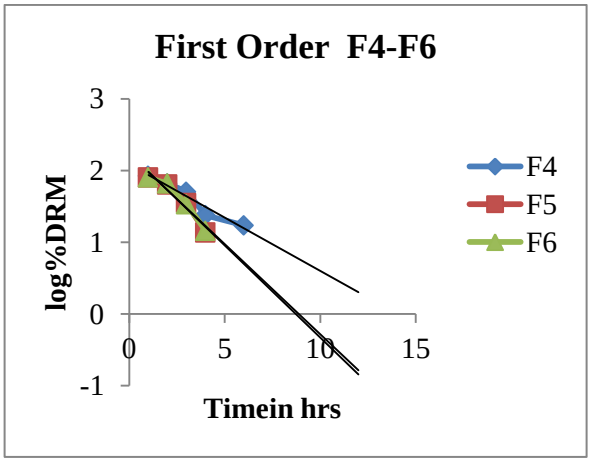

Fig: 12 First Order F4-F6

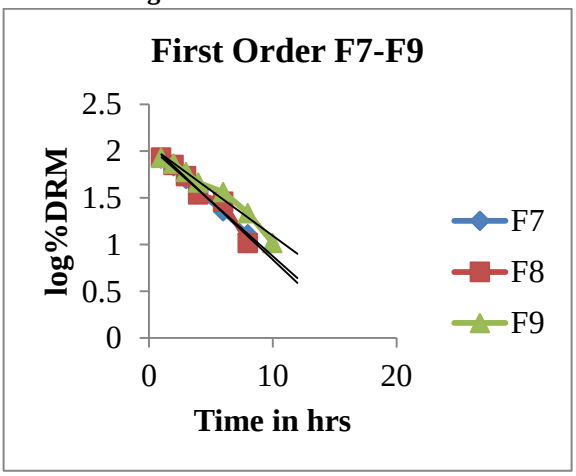

Fig: 13 First Order F7-F9

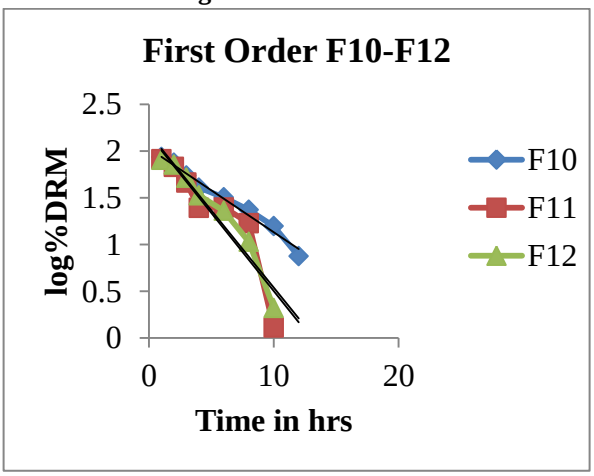

Fig: 14 First Order F10-F12

HIGUCHI ORDER KINETIC GRAPHS FOR ALL FORMULATIONS F1-F12

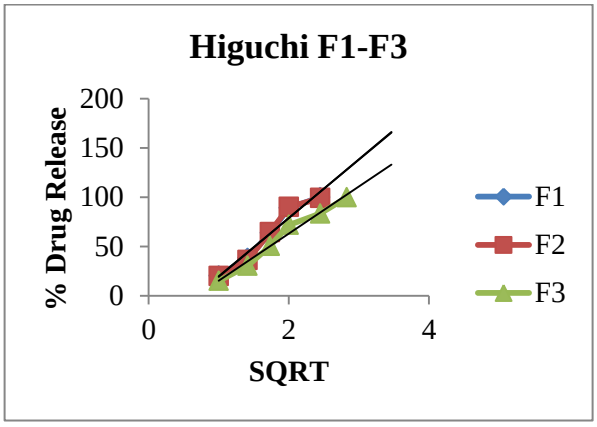

Fig: 15 Higuchi Order F1-F3

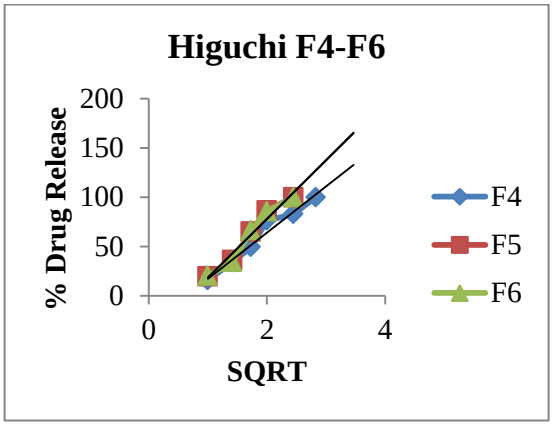

Fig: 16 Higuchi Order F4-F6

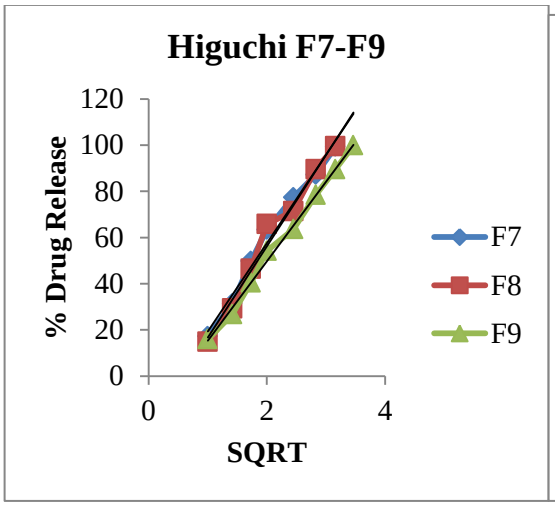

Fig:17 Higuchi Order F7-F9

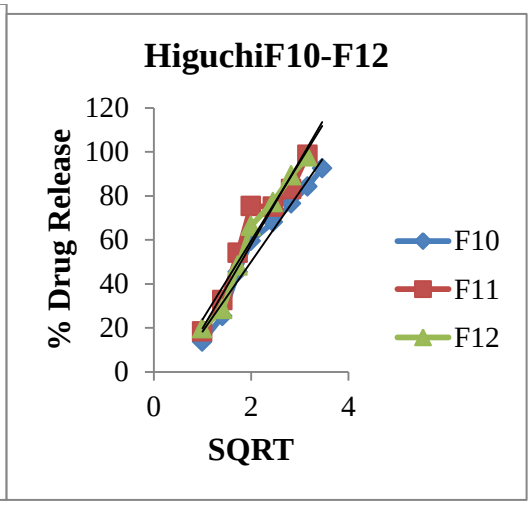

Fig: 18Higuchi Order F10-F12

PEPPAS ORDER KINETIC GRAPHS FOR ALL FORMULATIONS F1-F12

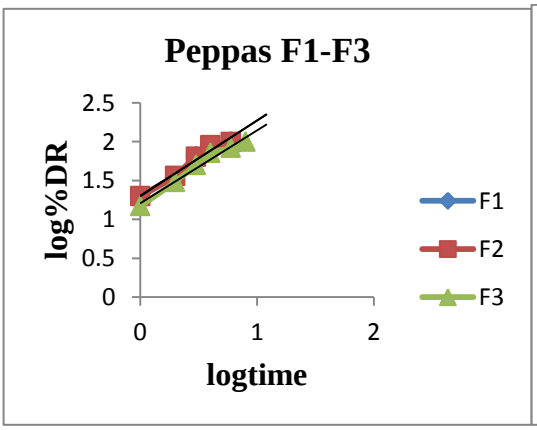

Fig: 19 Peppas Order F1-F3

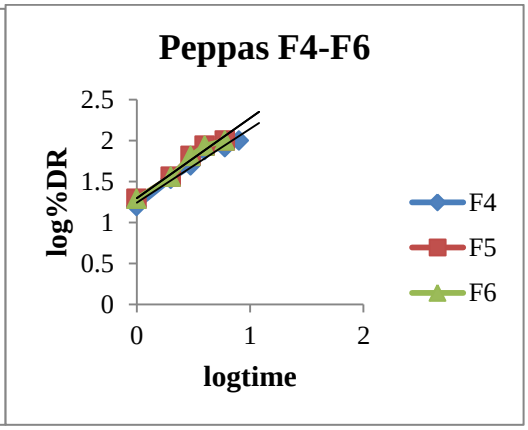

Fig: 20 Peppas Order F4-F6

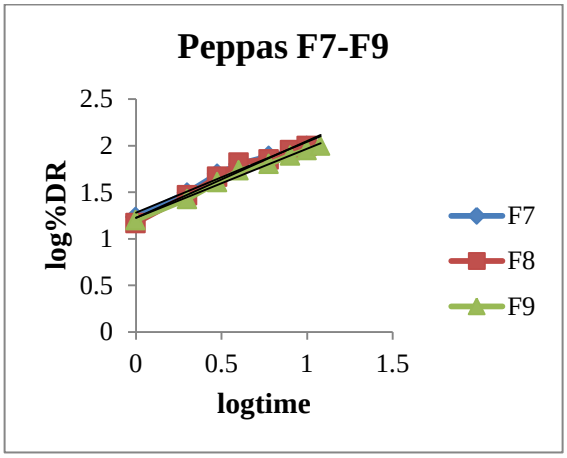

Fig: 21 Peppas Order F7-F9

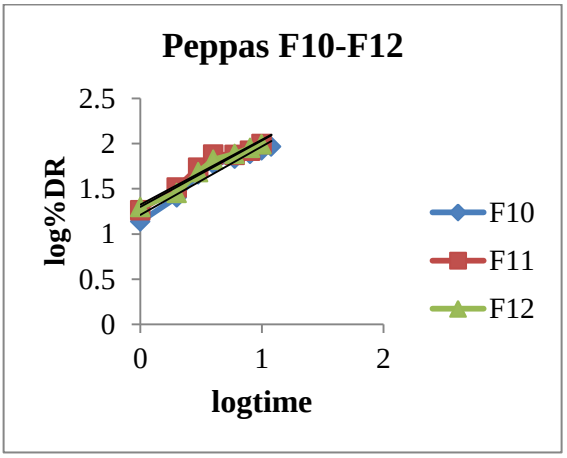

Fig: 22 Peppas Order F10-F12

KINETICS RELEASE DATA FOR NAPROXEN RELESE

FIRST ORDER KINETIC GRAPHS FOR ALL FORMULATIONS F1-F12

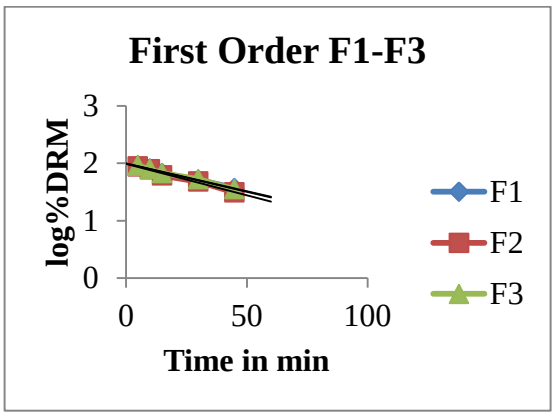

Fig: 23 First Order F1-F3

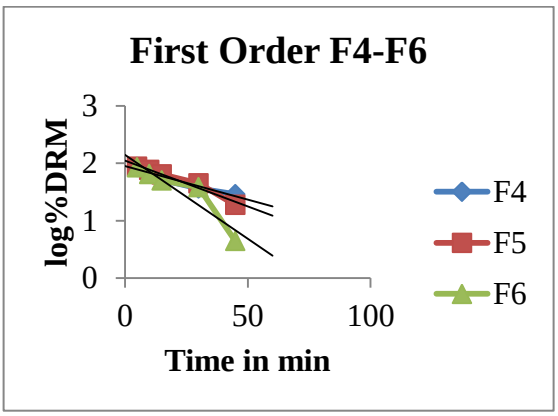

Fig: 24 First Order F4-F6

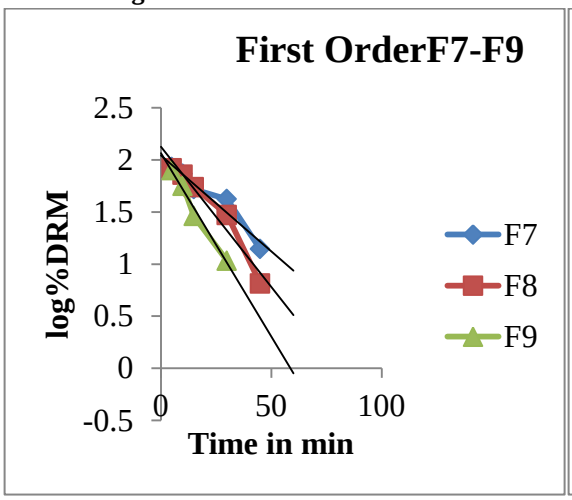

Fig: 25 First Order F7-F9

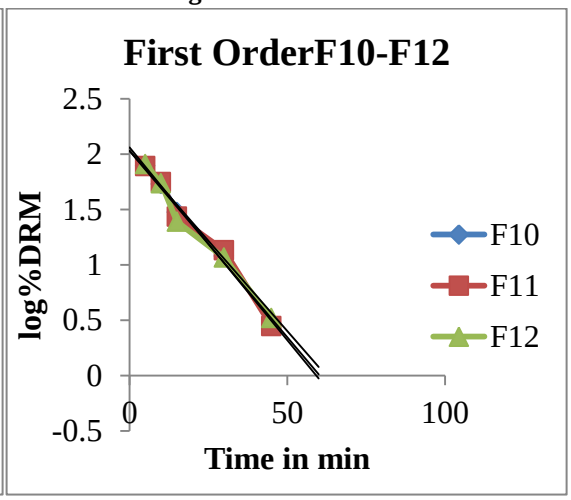

Fig: 26 First Order F10-F12

ZERO ORDER KINETIC GRAPHS FOR ALL FORMULATIONS F1-F12

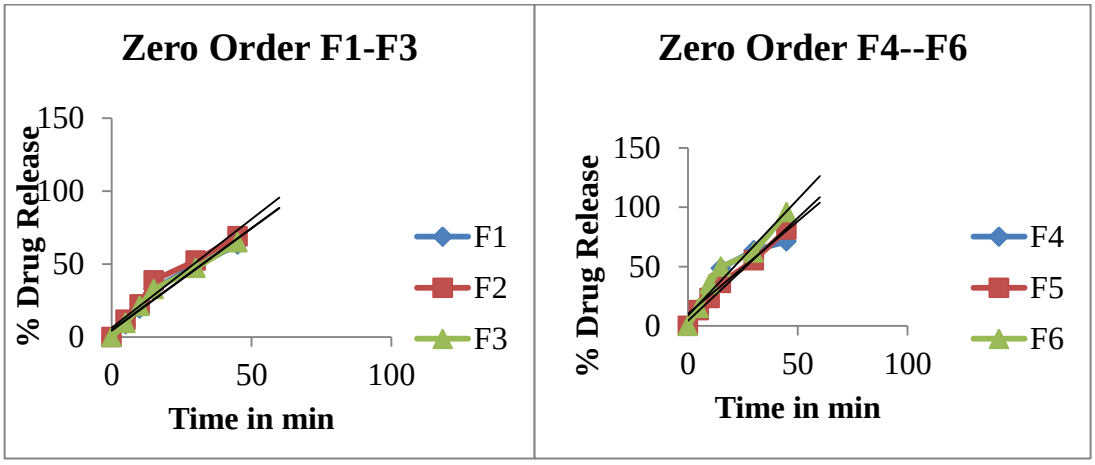

Fig: 27 Zero Order F1-F3

Fig: 28 Zero Order F4-F6

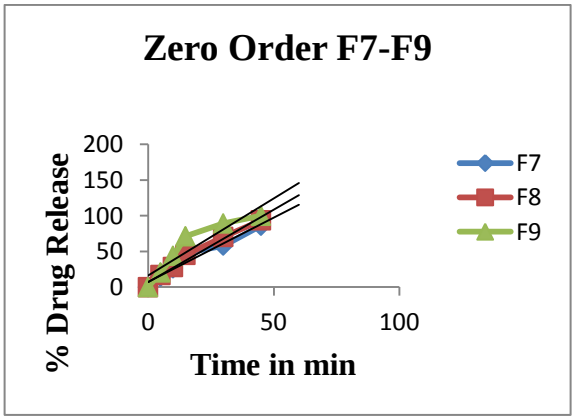

Fig: 29 Zero Order F7-F9

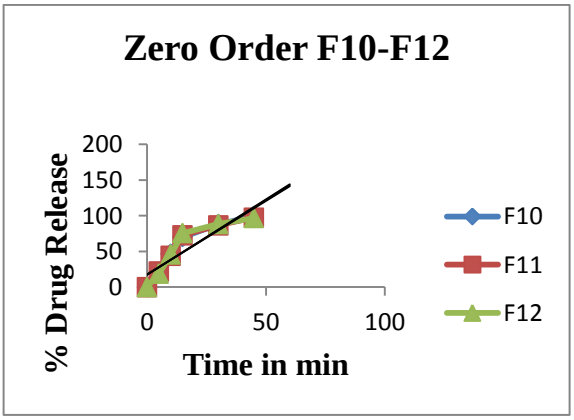

Fig: 30 Zero Order F10-F12

CONCLUSION

The formulation of combination porous tablets containing SS and NS was developed and evaluated.

The drug release pattern clearly indicated that the plasma levels of SS and NS simultaneously will be constant for a reasonable period of time. No drug–drug and drug–excipient interactions were observed. IR spectroscopic studies indicated that there are no drug-excipient interaction in the optimized formulation. The optimized formulation F_9 can be considered as a promising Immediaterelese delivery system of Naproxen providing nearly First order drug release over a period of 45 min and sustained delivery of Sumatriptan providing zero order drug release over period of 12 hrs. Simplicity of the formulation, ease of manufacturing and complete dissolution of system is among the advantages of the developed combination porous formulations.

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