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DEVELOPMENT AND EVALUATION OF KETOPROFEN MINI-MATRICES AS SUSTAINED RELEASE FORMULATION

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ABSTRACT

Mini-matrices (multiple unit dosage forms) with release sustaining properties were developed by simple extrusion (die cavity of 3 mm) using ketoprofen a NSAID as a model drug and hydrophilic (HPMC and xanthan gum), hydrophobic (ethyl cellulose) as a sustained release agents and 5% propylene glycol was selected as plasticizer with 10% lactose as channeling agent.

In vitro drug release study was calculated for all the formulations and showed maximum drug release of 93.81% for mini-matrices (F_{15}) having HPMC as polymer in a ratio of 1 : 2 with respect to drug along with plasticizer and channeling agent. The drug release has shown first order kinetics with diffusion release systems followed by erosion mechanism. The physico-chemical chracterization of mini-matrices were carried out by performing drug content, weight variation test, friability and uniformity of size. The FT-IR studies have showed no chemical interaction and drug was in an intact form.

The SEM studies were carried out to confirm the plasticizing efficiency of propylene glycol. Short term stability studies of all the parameters were done at a temperature of 30 ± 2ºC and 65 ± 5% RH and these were stable upto 3 months.

Keywords : Ketoprofen, HPMC, EC, Xanthan gum, Mini-matrices, Sustained release.

INTRODUCTION

The development of oral sustained and controlled release formulations offer benefits like controlled administration of a therapeutic dose at the desired delivery rate, constant blood levels of the drug, reduction of side effects minimization of dosing

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frequency and enhancement of patient compliance[1].

A distinction can be made between monolithic and microparticulate sustained release formulations. The main advantage of a microparticulate dosage form retaining to its *in vivo* behavior because the sub-units spread into the gastrointestinal tract as soon as the hard gelatin capsule or tablet disintegrates and hence, drug release occur over a large area avoiding high local drug concentrations. In addition, less inter and intra-subject variability can be expected as well as the decreased risk of dose dumping[2].

Ketoprofen [2- (3-benzoyl phenyl) propionic acid] is a non-steroidal anti-inflammatory drug (NSAID). It is potent inhibitor of cyclo-oxygenase enzyme resulting in the blockage of prostaglandin synthesis. It is used in musculoskeletal and joint disorders such as osteoarthritis, rheumatoid arthritis, alkylosing spondylitis, acute gout, abdominal cramps associated with menstruation and also shows analgesic-antipyretic activity[3, 4]. Its biological half-life is approximately 1.5-2 hours[5]. In adult, dose is approximately 25-50 mg, thrice a day (tid)[3].

The concept of mini-matrices for sustained release has evolved, which gives the advantage of a multiparticulate-sustained release formulation with predictable uniform gastric emptying time[2, 6] and use of hydrophilic and hydrophobic mini-matrices to produce MUDFs giving distinct advantages over SUDFs e. g. uniform plasma level and reproducible bioavailability. In addition, the mini-matrices have dosing flexibility[7].

EXPERIMENTAL

Materials and methods

Materials

Ketoprofen was a gift sample from M/s Shreya Life Sciences Pvt. Ltd., Aurangabad. Hydoxy propyl methyl cellulose and ethyl cellulose (Loba Chemie Pvt. Ltd., Mumbai) and xanthan gum (Hi-Media Laboratories Pvt. Ltd.), Mumbai were procured from commercial sources.

Methods

Preparation of mini-matrices[8, 9]

Ketoprofen : HPMC in a ratio of 1 : 1 were accurately weighed and passed through a sieve with an aperture of # 85. The mixture was triturated thoroughly in a mortar and was again passed through sieve # 85. Adding ethanol (70%) dropwise to the above mixture

with continuous trituration till a dough mass was achieved.

The dough mass was passed through the die cavity of extruder (which was fabricated at lab scale) to achieve elongated rod shaped mass (Fig. 1).

The elongated rod was subjected to air drying for 72 hrs on glass plates. The air-dried elongated rod was cut into units of 3 mm length mini-matrices with the help of suitable cutter.

The above procedure was repeated to prepare mini-matrices by using various polymers in different ratios as shown in Table 1.

Fig. 1(a) : Simple scale lab extruder

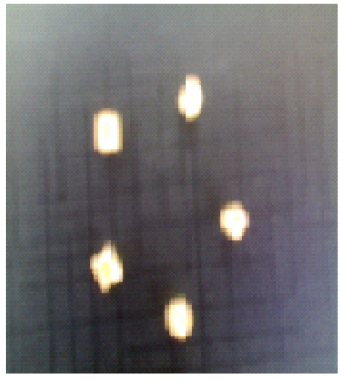

Fig. 1(b) : Mini matrices

Table 1 : Formulation of mini-matrices by simple extrusion method

Formu-lation code	Ketoprofen (mg)	HPMC (mg)	EC (mg)	Xanthan gum (mg)	Lactose (10% w/w)	Propylene glycol (5% w/w) 100	Solvent (ethanol)
F1	1000	1000	-	-	-	-	75%
F2	1000	1500	-	-	-	-	75%
F3	1000	2000	-	-	-	-	75%
F4	1000	-	1000	-	-	-	90%
F5	1000	-	1500	-	-	-	90%
F6	1000	-	2000	-	-	-	90%
F7	1000	1000	1000	-	-	-	90%
F8	1000	1500	1500	-	-	-	90%
F9	1000	2000	2000	-	-	-	90%
F10	1000	-	-	1000	-	-	50%
F11	1000	-	-	1500	-	-	50%
F12	1000	-	-	2000	-	-	50%
F13	1000	1000	-	-	200	100	75%
F14	1000	1500	-	-	250	125	75%
F15	1000	2000	-	-	300	150	75%

Determination of ketoprofen λ_{max} in methanol

Stock solution

Accurately weighed quantity of 100 mg ketoprofen was taken in 100 mL volumetric flask and was dissolved by using 5 mL of methanol. Finally the volume was made up with methanol upto 100 mL to produce 1 mg/mL of solution.

Scanning

A series of concentrations i. e., 2, 4, 6, 8, 10 and 12 μg/mL were prepared by using above stock solution and scanned between 200-400 nm. The absorption maxima of 255 nm was selected and used for further studies.

Physical parameters

Uniformity of weight[4,10] : All the prepared mini-matrices were subjected for weight uniformity test. In this test, 20 units of mini-matrices was weighed individually and average weight was calculated from, which percentage deviation was determined.

Friability test[4, 10] **:** All the prepared mini-matrices were evaluated for friability. In this test, 10 mini-matrices were taken and dedusted. All the 10 mini-matrices were weighed (W_I). The mini-matrices were placed in the drum of friabilator and was rotated at 25 ± 1 rpm for 100 time, after, which the mini-matrices were removed, dedusted and weighed (W_F). The percentage friability was calculated by using the formula :

$$\text{Percentage friability} = \frac{W_I - W_F}{W_I} \times 100$$

A maximum loss of weight NMT 1% is acceptable.

Uniformity of size

The diameter and length of all the formulations were measured using Vernier caliper.

Drug content[11]

The drug content was carried out in triplicate for all the formulations. Accurately weighed mini-matrices containing equivalent to 100 mg of ketoprofen were triturated and suspended in methanol using 100 mL volumetric flask. The solution was kept aside for 48 hours. After 48 hours, the solution is stirred for 5 minutes and filtered. Filtrate was suitably diluted to achieve a concentration of 6 mcg/ mL and was analyzed at 255 nm using Shimadzu-1700 UV-visible spectrophotometer against methanol as blank.

In vitro release study[12, 13]

The *in vitro* release of drug from mini-matrices were carried out for 12 hours using basket type electrolab tablet dissolution apparatus USP XXIII.

Mini-matrices were placed in capsule, which consists of drug equivalent to 300 mg. For the first 2 hours, pH 1.2 HCl buffer was used and was replaced with pH 7.2 phosphate buffer for another 10 hrs; the dissolution media was maintained at 37ºC ± 0.5ºC and a speed of 50 rpm. At prefixed time interval (every 1 hour), 5 mL of solution was withdrawn and replaced with 5 mL of fresh buffer, solution. After suitable dilutions, the samples were analyzed at 258 nm and 260 nm for HCl and phosphate buffer, respectively using Shimadzu-1700 UV visible spectrophotometer (Fig 2).

Statistical analysis[14, 15]

Statistics is a logic, which makes use of mathematics in the science of collecting, analyzing and interpreting data for the purpose of making decisions. Now, after many evaluations carried out on all the formulations of mini-matrices, the data obtained were subjected to statistical analysis. A computer aided calculations were done by using a preprogrammed software (Instat).

Characterization of mini -matrices

Scanning electron microscopy (SEM)[6, 16]

The surface morphology of the mini-matrices was examined using scanning electron microscopy. The samples were mounted directly into the SEM sample holder using double-sided sticking tape and were gold spray-coated

Fourier transformation infrared (FTIR) spectroscopy[17]

The drug-polymer and polymer-polymer interaction were studied by FTIR spectroscopy. Two percent (w/w) of the sample with respect to potassium bromide (KBr, Sd Fine Chem Ltd., Mumbai, India), was taken and mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 psi. Each KBr disc was scanned 16 times at 2 mm/sec at a resolution of 4 cm^{-1} using cosine apodization. The characteristic peaks were recorded and are shown in Fig. 5.

Stability study[18]

The purpose of stability study is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and to establish a retest period for the drug substance or a shelf-life for the drug product and recommended storage conditions.

The stability study of the selected formulations of ketoprofen mini-matrices were carried out according to ICH guidelines. The mini-matrices were placed in amber colored screw capped bottle for a period of 3 months at 30 ± 2ºC temperature and 65 ± 5% RH using stability chamber (Thermolab, Mumbai). Sampling was carried out at 30 days interval and was analyzed for all the parameters.

RESULTS AND DISCUSSION

Physicochemical properties

All the prepared mini-matrices were evaluated for physicochemical parameters like drug content, friability, weight uniformity and thickness. The prepared mini-matrices were having a 3 mm of diameter and thickness showing uniformity of size for all the formulations. The friability was carried out by using Veego friabilator and was found to have less than 1% friability. The weight uniformity was carried out by weighing individual 20 tablets and percent deviation was calculated, which was not more than 10% as per IP.

In vitro drug release

All the formulated mini-matrices were subjected for *in vitro* drug release study using USP XXIII dissolution apparatus for a period of 12 hours.

For the first 2 hours, pH 1.2 HCl buffer was used and replaced with pH 7.2 phosphate buffer for another 10 hours, which was maintained at 37 ± 2ºC, 50 rpm and drug release was analyzed at 258 nm and 260 nm, respectively. The percent drug release at 12 hours was found to be for hydroxy propyl methyl cellulose (HPMC) F_1 (82.59%), F_2 (82.36), F_3 (86.18%) and for ethyl cellulose (EC) F_4 (57.68%), F_5 (66.88%), F_6 (69.57%) and for HPMC-EC i. e., F_7 (65.98%), F_8 (70.24%), F_9 (58.57%), while for xanthan gum F_{10} (54.76%), F_{11} (77.20%) and F_{12} (53.41%).

Mini-matrices prepared by using HPMC showed a highest percent drug release as compared to mini-matrices prepared by using EC, HPMC-EC and xanthan gum.

Mini-matrices prepared by using HPMC (F_1, F_2 and F_3), which showed highest percent drug release were further modified into F_{13}, F_{14} and F_{15} by addition of 5% propylene glycol as plasticizer and 10% lactose as channeling agent

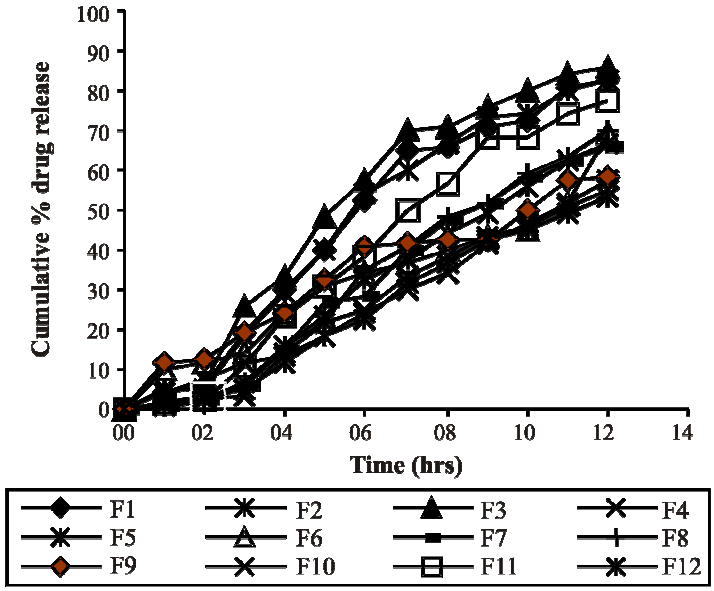

Fig. 2 (a) : Normal distribution curve of mini-matrices (F_1-F_{12})

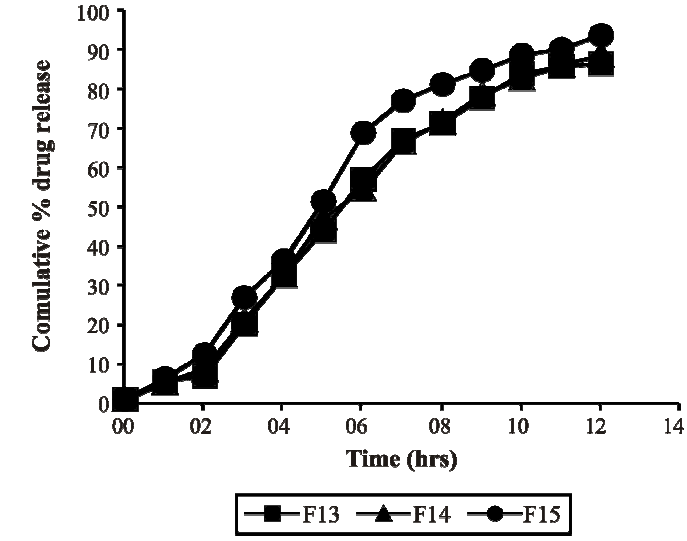

Fig. 2(b) : National distribution curve of mini-matrices F_{13}-F_{15} (prepared using plasticizer and channeling agent)

The *in vitro* drug release was carried out for F_{13}, F_{14} and F_{15}, which showed

86.40%, 88.65% and 93.81 percent drug release at 12 hours, respectively. Formulation F_{15}, which was prepared by using HPMC with 5% plasticizer and 10% channeling agent showed a highest percent drug release of 93.81% at 12 hours, when compared to other formulations.

The data obtained of all the formulations after *in vitro* release was subjected to statistical analysis by using a preprogrammed software (Instat). According to 'r' and 'slope' value, the *in vitro* release obeyed first order kinetics and mechanism of release was mainly through diffusion followed by erosion (anomalous behaviour).

SEM Studies

The SEM studies of formulation F_3 and F_{15} were done by using SEM LEO 14 SSVP. The SEM images of formulation F_{15} were compared with SEM images of formulation F_3, the formulation F_{15} showed reduction in air entrapment and increased wettability, which may be due to plasticizing property of propylene glycol as shown in Figs. 3-4

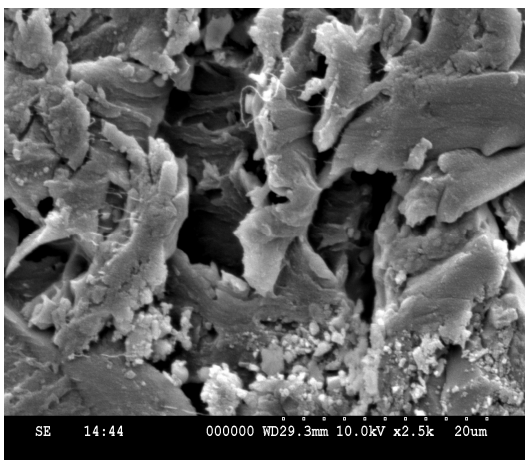

Fig. 3 : Scanning electron micrograph of formulation F_3 (without plasticizer and channeling agent)

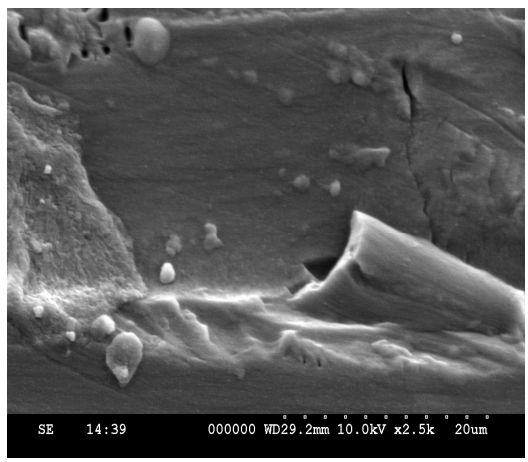

Fig. 4 : Scanning electron micrograph of formulation F_{15} (prepared using plasticizer and channeling agent)

IR Studies

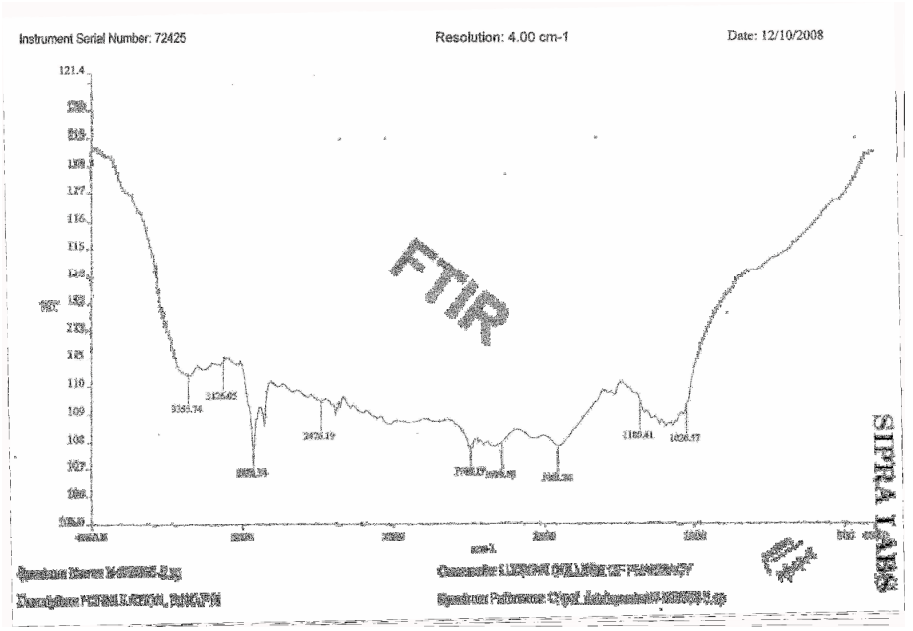

Fig. 5(a)

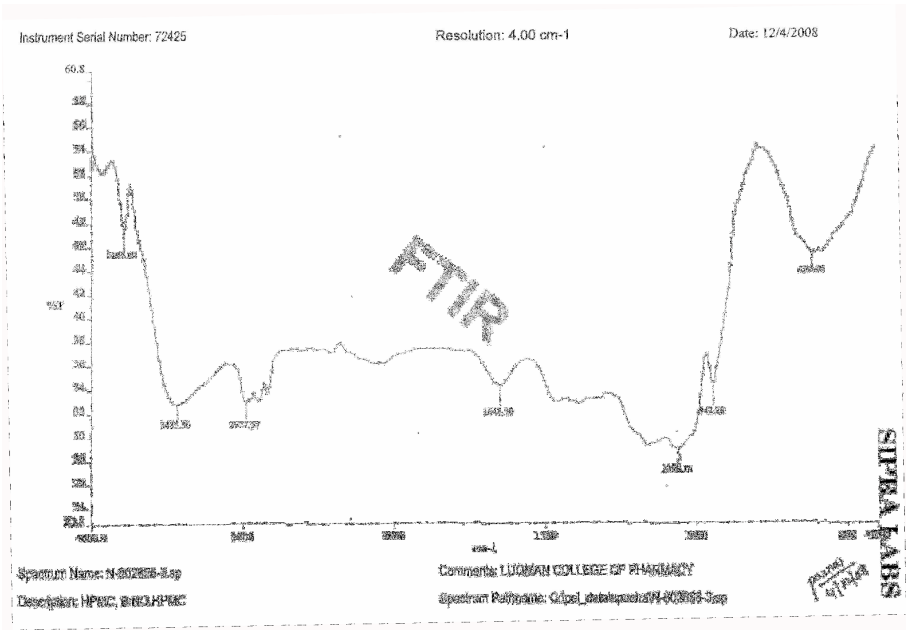

Fig. 5(b)

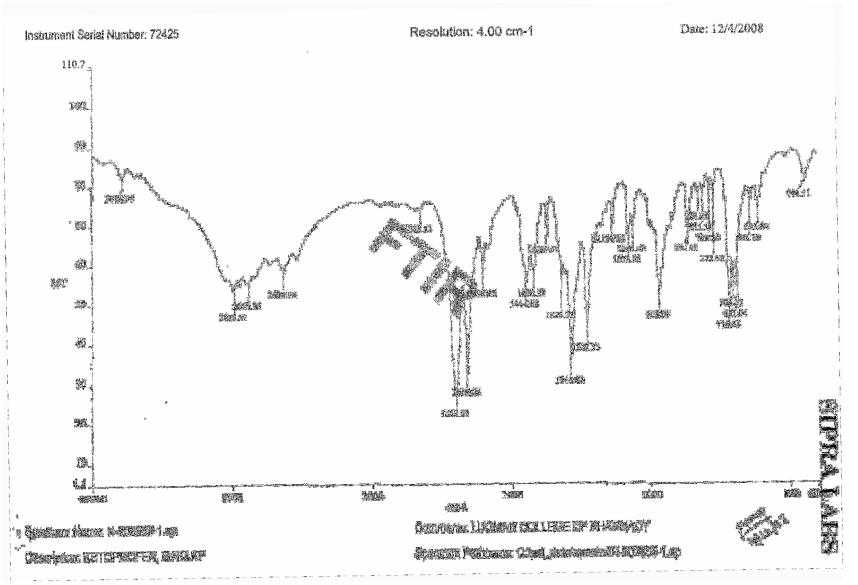

Fig. 5(c)

Fig. 5 : Drug-polymer interaction (IR studies) of plain ketoprofen (a), HPMC (b) and F_{15} (C)

The interactions between drug-polymer and polymer-polymer were confirmed by Fourier-transform infrared (FTIR) spectroscopy. The FTIR spectra of ketoprofen, HPMC, F_{15} were recoded and represented in Fig. 5.

Ketoprofen IR spectrum exhibited two significant absorption peaks at 1697 and 1655 cm^{-1} due to carbonyl group of carboxylic acid. In ketoprofen, which is sandwiched between two aromatic rings shows significant C–H peaks are observed from 2817 cm^{-1} to 2990 cm^{-1} range. The polymer HPMC shows broad absorption peak at 3435 cm^{-1} due to the number of OH groups present in the molecule. A number of C–H peaks are also observed from 2800 to 2990 cm^{-1}

The IR of formulated F_{15}, which was prepared by using the drug and HPMC was recorded, which showed that none of the peaks due to the OH absorption of HPMC and C=O absorption of drug were disturbed; thus, indicating no chemical reaction between the ketoprofen and HPMC. It means that drug is available in the free form for its biological effects to be used.

From the above experiments, one can conclude that ketoprofen can be used to formulate mini-matrices without undergoing any chemical change using HPMC, lactose and propylene glycol. Lastly, along with ethyl cellulose, HPMC-EC or xanthan gum, in all these cases, drug is present in the free form.

Stability studies

All the parameters evaluated during stability studies indicated that all the formulations were stable.

CONCLUSION

Simple extrusion technique can be used to produce mini-matrices for sustained drug delivery. According to the release studies, HPMC was most suitable along with lactose (channeling agent) and propylene glycol (plasticizer) to sustain the release for 12 hours.

The release mechanism for all batches of mini-matrices followed anomalous diffusion transport and showed first order kinetics. The SEM studies confirmed the efficiency of plasticizer and channeling agent. Due to presence of plasticizer and channeling agent, drug release has been increased upto 7.63%.

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