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"FORMULATION AND EVALUATION OF EFFERVESCENT TABLETS OF NSAID AGENT"

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ABSTRACT

The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus onset of action is prolong. This can be overcome by administrating the drug in liquid from but, many APIs have limited level of stability in liquid form. So, Effervescent Tablets acts as an alternative dosage form. The tablet is added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The tablet is quickly broken apart by internal liberation of CO_2 in water due to interaction between tartaric acid and citric acid with alkali metal carbonates or bicarbonates in presence of water. Due to liberation in CO_2 gas, the dissolution of API in water as well as taste masking effect is enhanced. The advantages of effervescent tablets compared with other oral dosage forms includes an opportunity for formulator to improve taste, a more gentle action on patient's stomach and marketing aspects. In present work an attempt has been made to formulate an effervescent tablet containing immediate release of analgesic and antipyretic drug using various acids and bases. In present work we are used different acids and bases in different concentration**.** In the preformulation study, compatibility evaluation was performed which implies that drug; acids, bases and other excipient are compatible with each other. The formulation of tablets was done by using wet granulation as well as dry granulation in that technique wet granulation which was found acceptable**.** The total nine placebo tablets were prepared and evaluated for hardness, disintegration time, weight variation and solubility. All the formulation shows hardness and weight variation with in limit but the combination of citric acid (12.56%), tartaric acid (25.17%), sodium bicarbonate (38.20%), sodium carbonate (6.41%) ,binding agent PVP-K-30 (2.94%) and sodium benzoate (0.52%). for the final

formulation, (F7) Because these ingredients shows the good effervescent reaction and has no problem in capping and sticking like other formulation.

KEYWORDS: NSAID Agent, Effervescent tablet, Binding agent-PVP-K-30.

INTRODUCTION

Effervescent tablet

The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus onset of action is prolong. This can be overcome by administrating the drug in liquid from but, many APIs have limited level of stability in liquid form. So, effervescent tablets acts as an alternative dosage form. The tablet is added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The tablet is quickly broken apart by internal liberation of CO_2 in water due to interaction between tartaric acid and citric acid with alkali metal carbonates or bicarbonates in presence of water.

The aim of this study is to develop and physico-chemically evaluate the Effervescent Tablets of analgesic and antipyretic drug. To enhance the onset of action of analgesic and antipyretic drug and increase the solubility of analgesic and antipyretic drug. Conventional tablets are often assosiate with slower onset of action and also undergoes first pass metabolism. Effervescent tablet avoid the first pass metabolism and also produce rapid onset of action. Oral liquid also provide rapid onset of action but required carefully handling.

METHODS AND MATERIALS

API was procured by Shri krishna pharmaceuticals (Mumbai,India), Citric acid, Sodium citrate (anhydrus), Fumaric acid, Sodium Benzoate was gifted by Thomas baker (Mumbai, India), Tartaric acid, Sodium bicarbonate (anhydrous), Sodium citrate was gifted by Lar Chemical (Mumbai, India), Ascorbic acid, Mannitol was gifted by Bajaj Health Care. Ltd (Mumbai, India), Polyethylene Glycol-6000, Polyvinylpyrolidone-K-30 was gifted by Nan Hang Industrial Co-Ltd, Simethicone was gifted by Nouvveaw Exports Pvt.Ltd, (Mumbai, India), Acesulfame Potassium was gifted by Shanghai fortune was Co.Ltd. China.

Preformulation

Pre-formulation is a branch of pharmaceutical sciences that utilizes biopharmaceutical principles in the determination of physicochemical properties of a drug substance. The goal

of pre-formulation studies is to choose the correct form of the substance, evaluate its physical properties and generate a through understanding of the material's stability under various conditions, leading to the optimal drug delivery system. the preformulation study focuses on the physiochemical parameters that could effect the development of efficacious dosage form. these properties may ultimately provide a rationale for formulation design. also it will help in minimizing problems in later stages of drug development, reducing drug development costs and decreasing product's time to market. it gives the information needed to define the nature of the drug substance and provide framework for the drug combination with pharmaceutical excipients in the dosage form.

i. Bulk Characterization

ii. Solubility Analysis

iii. Stability Analysis

Spectral identification

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, to promote the consistent release and bioavailability of the drug and protect it from degradation.

Infra red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

In the present study, the potassium bromide disc (pellet) method was employed. Chemical stability was confirmed by IR spectrometry.

The results are shown in Figure. No: 2-4

A. Evaluation of Granules of Model Drug

- Angle of repose
- Bulk density
- Tapped density
- Compressibility

I) Evaluation of Granules

The ideal characteristics of a tablet that make it a popular and acceptable dosage form are compactness, physical stability, rapid production capability, chemical stability and efficacy.

In general above characteristics of tablet are dictated by the quality of the granulation from which it is made. Many formulation and process variables involved in the granulation step can affect the characteristics of the granulation produced. Therefore various methods to measure certain granulation characteristics have been developed to monitor granulation suitability for tableting. The main characteristics required to be monitored in granulation are flow properties and compressibility.

i. angle of repose:
ii. apparent bulk density: (δu)
iii. packed bulk density: (δb)
iv. percent compressibility: (%c)

Evaluation of Effervescent Compressed Tablets

- tablet shap
- e & dimensions
- hardness
- thickness
- friability
- weight variations
- disintegration time
- content uniformity of active ingredients
- in-vitro drug release
- comparison with marketed conventional tablet

Preformulation study

To ensure the compatibility of drug with excipients the IR spectra for pure drug and prepared granules was obtained and were compared for ensuring no change in the principle peaks - non interference and possible degradation.

The peaks obtained in prepared granules of formulations were almost identical to those obtained for pure drug reveling that there was no interaction between drug and acids bases and other ingredients.

Direct Compression

Table No.1Composition of Effervescent Tablets of Model Drug(Direct Compression)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
model drug	650	650	650	650	650	650	650	650	650
citric acid (anhydrous)	231.63	104.5	525	520	485	485	490	480	480
tartaric acid	-	201	1045	1045	982	982	982	970	960
ascorbic acid	-	-	-	-	-	-	-	-	-
fumaric acid	191.96	-	-	-	-	-	-	-	-
sodium bicarbonate	277.86	352.5	1577	1574	1483	1483	1483	1400	1350
sodium carbonate	-	-	265	265	250	250	250	240	210
sodium citrate	200	-	20	-	-	-	-	-	-
sodium benzoate	-	-	-	18	10	15	20	25	30
Mannitol		208	208	208	220	225	-	-	-
peg-6000	30	20	-	-	40	-	-	-	-
pvp-k-30	15	18	20	60		60	115	80	100
acesulphum potassium	-	-	10	20	20		30	20	15

Wet Granulation

The Wet granulation process performed into three steps.

Dry Mixing & Granulation

Lubrication of Granules

Compression of Lubricated Granules

Dry Mixing & Granulation

There are two steps in dry mixing & granulation process i.e. Acid granulation & base granulation.

1) **Acid granulation**

(i) In first step Weight the Citric acid, Tartaric acid were blended and passed through Sieve No.# 40.

(ii) In second step simethicone was dissolved in organic solvent i.e.methylene chloride.

The above organic solvent was mixed with acid portions i.e. citric acid & tartaric acid. The obtained wet mass passed through sieve no.# 20 & kept in tray dried at 60^0c for 1 hr.until the L.O.D.was observed about below 1%. (On IR at 105^0C for 5 minutes).

2**) Base granulation**

(i) In base granulation firstly the sodium bicarbonate, sodium carbonate were blended and passed through sieve no.# 40.

(ii) In the second step the binding agent PVP-K-30 was dissolved in organic solvent i.e. methylene chloride.

The above organic solvent was mixed with base portions i.e. sodium bicarbonate & sodium carbonate. The obtained wet mass passed through sieve no.# 20 & kept in tray dried at 60^0c for 1 hr.until the L.O.D.was observed about below 1%. (On IR at 105^0C for 5 minutes).

Lubrication of acid and base granules

after drying at R.T.of both granules i.e. acid granules and base granules were mixed. After mixing of both granules the MODEL DRUG, Acesulphum potassium and lubricating agent sodium benzoate add to the granules and well mixed.

Compression of Lubricated Granules

The Lubricated granules were compressed into tablet by using Single rotary tablet Punching machine, 12 stations, with 24.8mm punch sets.

Table No.2Composition of Effervescent Tablets of Model Drug Model Drug(Wet Granulation)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Model drug	650	650	650	650	650	650	650	650	650
citric acid (anhydrus)	231.63	104.5	525	520	485	485	490	480	480
tartaric acid	-	201	1045	1045	982	982	982	970	960
ascorbic acid	-	-	-	-	-	-	-	-	-
fumaric acid	191.96	-	-	-	-	-	-	-	-
sodium bicarbonate	277.86	352.5	1577	1574	1483	1483	1483	1400	1350
sodium carbonate	-	-	265	265	250	250	250	240	210
sodium citrate	200	-	20	-	-	-	-	-	-
sodium benzoate	-	-	-	18	10	15	20	25	30
Mannitol		208	208	208	220	225	-	-	-
peg-6000	30	20	-	-	40	-	-	-	-
pvp-k-30	15	18	20	60		60	115	80	100
Simethicone	-	-	-	15	15		60	25	50
acesulphum potassium	-	-	10	20	20		30	20	15

Stability studies

Stability testing forms an integral part of formulation development. It is important to assess the effect of temperature and humidity on stability of drug and in-vitro drug release rate. It helps to generate information for predicting the shelf life of the product and recommended storage conditions. Stability data is required to be submitted as part of the dossier submitted to the regulatory agencies.

The Results are shown in the table. No: 4-10.

RESULTS AND DISCUSSION

Prior to the formulation, preformulation study was carried out on drug and excipents. in the present work, formulation part divided into four steps. in first step, placebo tablets were made using different acids and bases in different concentrations. the detailed composition is shown in table. The granules were subjected to evaluation such as angle of repose, bulk density, tapped density. The placebo tablets were evaluated for various physical parameters such as thickness, hardness, friability, weight variation, disintegration, and solubility. from these best acid base combination and various other ingredients that are usually water-soluble were selected.

Table No-3 Standard Calibration Curve for Model Drug(P^H-1.2)

concentration mcg/ml	Absorbance
1	0.022
2	0.044
3	0.064
4	0.087
5	0.115
6	0.135
7	0.157
8	0.180
9	0.206
10	0.240

slope=0.0229 r^2=0.996

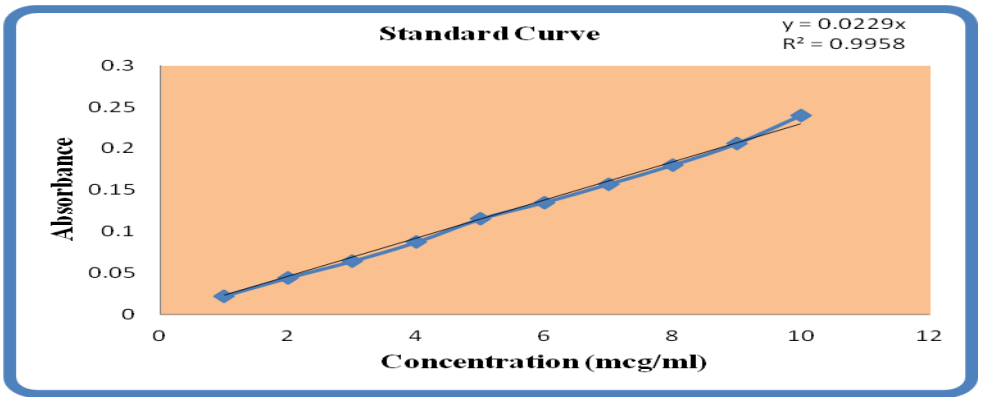

Fig.No.1-Standard Curve Of Model drug

Evaluation of Tablets

I) Tablet dimensions

Tablet dimension include thickness and diameter of tablet. five tablet of each formulation were evaluated and mean thickness values obtained are shown in table no.-.

the value indicates that, die fill was uniform and compression force was consistent.

II) Friability

Friability values are within acceptable limit, implying good compactness and strength of these formulation.

III) Average Weight And Weight Variation

Twenty tablets of each formulation were evaluated. the mean values and weight variation of each formulation are recorded in table no. the values obtained indicate that all the tablets of different formulations meet the ip/ u.s.p. requirements.

The observed narrow range weight variation indicates granule flow ability; desired packing characteristics and uniform dies fill of all the formulations. This is supported by the acceptable flow properties of granules obtained in the pre-formulation.

IV) Disintegration Time

The disintegration time test values are within acceptable limit. The acids and bases are used in 38% and 45% respectively in final formulation.

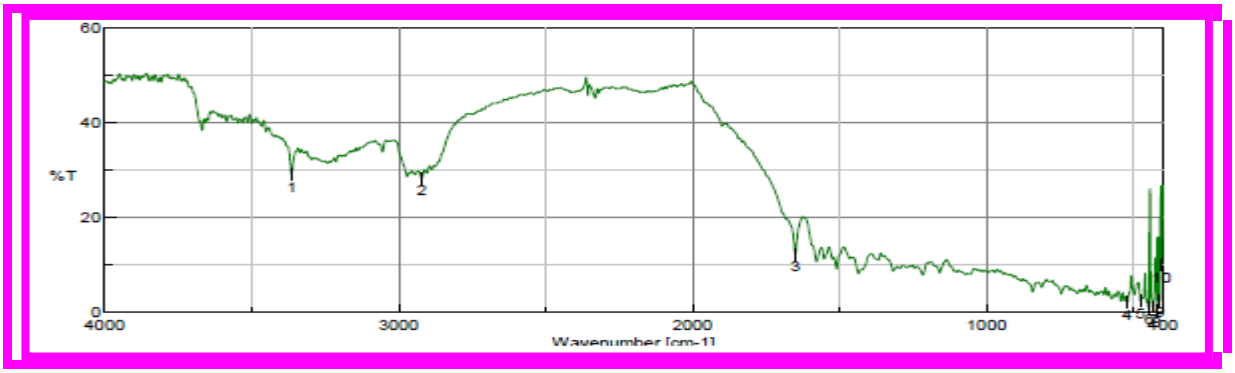

Fig.No.2- IR Curve of API (Model Drug)

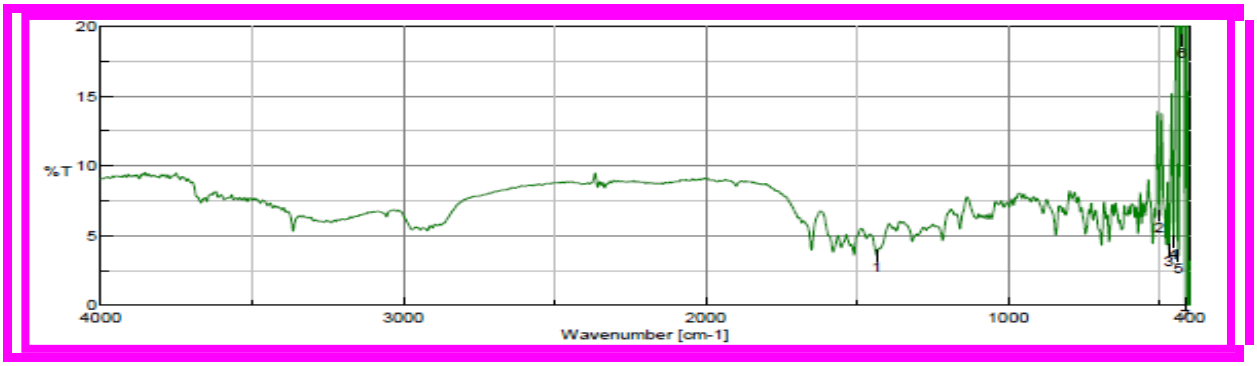

Fig.No.3- IR Curve of API (Model Drug) + Direct Compression Method

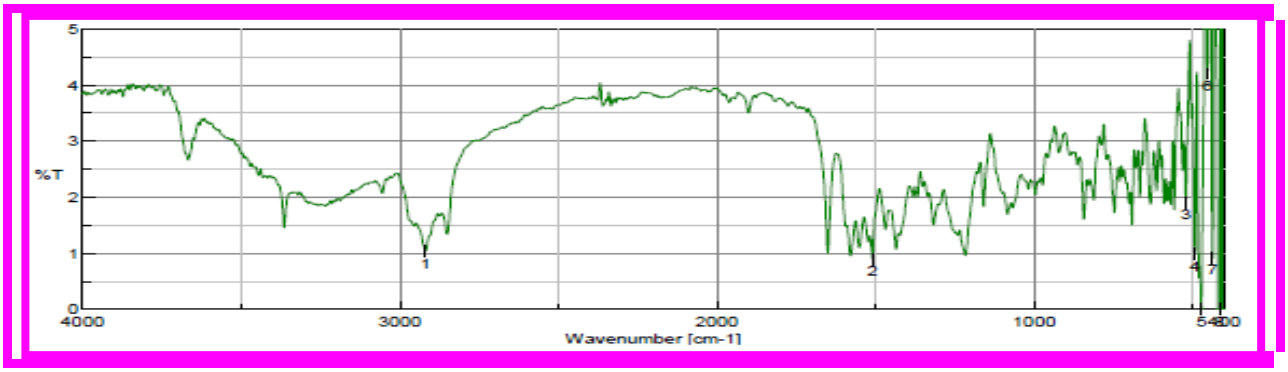

Fig.No.4- IR Curve OF API (Model Drug) + Wet Granulation

Stability studies

Accelerated stability testing

Table no:4- stability parameters of formulation F7stored at room temperature

PARAMETER	INITIAL	AFTER 15 DAYS	AFTER 30 DAYS
Drug Content (%)	98%	97.7%	96%

Table no.5.- Stability Study of In-Vitro Dissolution for Formulation F7 AT R.T.

TIME (MIN)	% DRUG RELEASE		
	INITIAL	AFTER 15 DAYS	AFTER ONE MONTHS
0	0	0	0
1	104.5	100.15	100.1
2	102.45	99.91	99.29
3	99.24	95.76	95.84
5	99.15	94.22	94.53

Table No.6- Stability Parameters of Formulation F7 Stored at Temperature 40^{O}C and RH 75%.

PARAMETER	INITIAL	AFTER 15 DAYS	AFTER ONE MONTHS
Drug content (%)	98%	97.7%	96%
In-vitro disint. Time (sec)	65	70	76

Table No.7- Stability Study of In-Vitro Dissolution for Formulation F7 Stored at Temperature 40^{O}C AND RH 75%

PARAMETER	INITIAL	AFTER 15 DAYS	AFTER ONE MONTHS
Drug content (%)	104.5%	97%	98%
In-vitro disint. Time (sec)	65	70	76

Table No.8- Properties of the Prepared Formulations

PROPERTY	FD1	FD2	FD3	FD4	FD5	FD6	FD7	FD8	FD9
Bulk Density, G/CM^3	0.50	0.52	0.52	0.58	0.66	0.66	0.625	0.58	0.58
Tapped density G/CM^3	0.588	0.76	0.71	0.71	0.83	0.90	0.7142	0.66	0.66
% Compressibility	14.96	31.57	26.76	18.30	20.48	27.67	12.50	13.13	13.13
Thickness (MM)	5.60	5.39	5.49	5.95	5.90	5.85	5.85	5.88	5.83
Disintegration Time (sec)	90	100	65	55	59	70	62	66	72
Water content (l.o.d.) %	1.8	1.8	1.8	1.6	3.4	1.4	1.0	1.2	1.4
Diameter (MM)	24.8	24.8	24.8	24.8	24.8	24.8	24.8	24.8	24.8

Table No.9 Effect of Acids and Bases On Effervescent Time of Tablets

PROPERTY	FD1	FD2	FD3	FD4	FD5	FD6	FD7	FD8	FD9
Thickness (mm)	5.60	5.39	5.49	5.95	5.90	5.85	5.85	5.88	5.83
Disintegration time, seconds	90	100	65	69	75	70	62	66	72
% Compressibility	14.96	31.57	26.76	18.30	20.48	27.67	12.50	13.13	13.13

Table. NO: 10 Marketed Samples I.E.Eno Fruit Salt, Histac Tablets

PROPERTY	FD7	MARKTED EFFERVESCENT SALT	MARKTED EFFERVESCENT TABLET
Bulk density (g/cm^3)	0.625	0.7142	0.5882
Tapped density (g/cm^3)	0.7142	0.7692	0.666
% Compressibility	12.50	7.15	11.62
Hardness (kg/cm^2)	3.9	_	4.7
Thickness (mm)	5.85	_	5.62
Disintegration time (sec.)	62	30	55
Water content (l.o.d.) %	1.0	0.7	0.8
Diameter (mm)	24.8	_	24.8
Co_2 content	0.63g/tab(16.34%)	19%	16.23%

SUMMARY AND CONCLUSION

The study was undertaken with an aim to formulate effervescent tablet of analgesic and antipyretic drug (model drug). The literature review showed that model drug having simmilar mechanism of action to aspirin because simmilarity in structure. model drug act by reducing production of prostaglandin which involved in pain and fever process, by inhibiting the cyclo-oxygenase enzyme.

In present work an attempt has been made to formulate an effervescent tablet containing immediate release of model drug using various acids and bases. In present work we are used different acids and bases in different concentration.

All the formulations were subjected to various evaluation studies. Result of the evaluation of granules and evaluation of tablet dimensions, hardness, friability, weight

variations.

In the effervescent tablet the water content can be measured by Karl Fischer titration method. We are also subjected to carbon dioxide content in the effervescent tablets. Uniformity in tablet dimensions implies that die fill was uniform and compression force was constant. Hardness values reveal that tablets are having good mechanical strength and handling characteristics. Friability values dictate good compactness of the formulations. The weight variation of all formulated tablets was satisfactory, attributed by the acceptable flow properties of granules. Content uniformity of active ingredient of all the formulations are within acceptable limit and ensures dosage uniformity. The promising formulation F7 obtained in evaluation studies.

The effervescent tablet can be prepared using different acids such as citric acid, tartaric acid, fumaric acid, and ascorbic acid in different concentration. In that also we are used the various lubricants and binding agents. There are 7 formulations that contain the citric acid, tartaric acid, sodium bicarbonate, and sodium carbonate. These 7 formulations evaluated for hardness, friability, and weight variation, effervescent time etc. all the formulation. All the formulation found effervescent upto 72 sec. But the formula having citric acid(12.56%),tartaric acid (25.17%),sodium bicarbonate(38.20%)and sodium carbonate(2.94%). So these concentration of acids and bases used for the final formulation.

The effervescent tablet were prepared by different preparation method such as Direct compression, wet granulation. The prepared tablets were evaluated for content uniformity and physical parameters. The direct compression was found there was an capping problem. So the upper surface of tablets not properly set. but with the help of wet granulation technique the powder become free flowing and the compression of the tablets so good as compaired to the direct compression reason behind the choosing the wet granulation because in dry granulation technique the capping and sticking problem occur. But by wet granulation technique the granules become good flowing properties as compaired to direct compression. Because wet granulation provides the acids and bases from the environmental moisture. And capping problem was reduced. At the time of manufacturing of effervescent tablet the strictly humidity and temperature should be maintained. the L.O.D.of the tablet should be less than 1%. Because if one-

water molecules present in the effervescent tablet then the obtained effervescent reaction of the tablet should be very less.

The stability study i.e. accelerated stability study according to I.C.H.guidelines can be performed i.e 40^0C ,75% RH. The stability can also be performed at R.T, 45°C, cold temperature i.e. 2-5°C. formulation showed no significant variations for the above mentioned parameters and it was stable for the specified time period.

From the above summary it was concluded that, the effervescent tablets of model drugcan be formulated for quick analgesic and antipyretic action by effervescence reaction using citric acid (12.56%), tartaric acid (25.17%), sodium bicarbonate (38.20%) and sodium carbonate (2.94%).gives the better effervescence. the PVP-K-30 used as the binding agent. sodium benzoate (0.5%) as lubricating agent.

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