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Formulation and Evaluation of Oral dispersible tablet of Tramadol Hydrochloride

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Abstract: The objective of the present study is to develop a pharmaceutically stable formulation of oral dispersible tablet of Tramadol hydrochloride . In this study oral dispersible tablets of Tramadol hydrochloride were prepared by Direct compression method. Several trial formulations i.e, from F1-F9 have been taken to optimize and develop a robust formulation. The study is to clarify the effect of different superdisintegrants like Crospovidone (CP)(F1,F2,F3), Croscarmellose sodium (CCS)(F4,F5,F6), Sodium starch glycolate (SSG)(F7,F8,F9) on disintegration and dissolution properties of the drug. The prepared tablets were evaluated for weight variation, wetting time, hardness, thickness, friability, % drug content, disintegration time, *in vitro* drug release and *in vivo* release study. Formulation F3 showed a drug release of 99.18% in 30mins which is faster than the other 2 superdisintegrants used in the study and also with the innovator product. The stability studies, shown that the formulation F3 was stable enough at 40°C / 75% RH for a period of 1 month. Th e comparision of pharmacokinetic parameters between the ODTs Tramadol HCl and conventional tablet, showed no major changes in the pharmacokinetic parameters. Therefore it can be concluded that the formulation F3 is robust and stable.

Keywords: Tramadol hydrochloride, crospovidone, Croscarmellose sodium, Sodium starch glycolate, In-Vitro drug release, In-vivo drug release.

Introduction:

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma(or at the site of action) and maintains it constant for the entire duration of treatment[1]. Drugs are frequently taken by oral administration, although a few drugs taken orally are intended to be dissolved within the mouth, majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered as most natural, convenient means of administering drugs[2].*Oral Dispersible Tablet* is an innovative tablet technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient[3,4]. Tramadol and its O-desmethyl metabolite (M1) are selective, weak OP3-receptor agonists. Opiate receptors are coupled with G-protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. As the effector system is adenylate cyclase and

cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline is inhibited. The most commonly reported adverse drug reactions are nausea, vomiting, sweating and constipation.

Materials and Methods:

Tramadol hydrochloride, Micro crystalline cellulose, sodium starch glycolate, crospovidone, Croscarmellose sodium, Aspartame were obtained as gift sample from KAPL, Bangalore. Other materials used were purchased from local vendor and were of analytical grade.

Experimental work:

Preparation Tramadol hydrochloride Tablets:

A mixture of Tramadol HCl and β-cyclodextrin (1:2)was ground in a glass container and a minimum amount of water was added and triturated for 15-30min to get the slurry and air dried at 40°c for 24hrs, pulverized and passed through sieve no:100 and stored in a dessicator over fused calcium chloride. The mixture was used for the preparation of tablets, all materials were passed through sieve no.40.Disintegrant was divided into two equal parts by weight. Drug complex was added to one part, and in another part aspartame was added. Then the materials were blended for 10mins.Then the Blended mass were sifted through 20/40 mesh screen. Ten percent of the fines were added to the mass and then blended for another 2 minutes. Then a weighted quantity of Aerosil and remaining superdisintegrant were added to the mass and blended for five minutes. The granules of the drug were compressed in a 16 station rotary compression machine using flat faced punches of 10mm diameter.

Table 1: Composition of Oral Dispersible tablet of Tramadol HCL (All quantities in mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug complex	151.2	151.2	151.2	151.2	151.2	151.2	151.2	151.2	151.2
Micro crystalline cellulose	116.3	110.3	104.3	116.3	110.3	104.3	116.3	110.3	104.3
Crospovidone	12	18	24	_	_	_	_	_	_
Croscarmellose	_	_	_	12	18	24	_	_	_
Sodium starch glycolate	_	_	_	_	_	_	12	18	24
Aspartame	6	6	6	6	6	6	6	6	6
Aerosil	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Talc	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mint flavour	3	3	3	3	3	3	3	3	3
Total weight of the tablet	300	300	300	300	300	300	300	300	300

Evaluation of powder blend:

Determination of bulk density and tapped density

Bulk Density:

Apparent bulk density (B.D) was determined by placing presieved drug excipients blend into a graduated cylinder and measuring the initial volume (Vo) weight of powder (W). The bulk density was calculated using the formula.

Bulk Density (B.D) = W / Vo

Tapped Density:

The measuring cylinder containing known mass of blend was tapped for a fixed number of taps. The

minimum volume (Vf) occupied in the cylinder and the weight of powder (W) was measured. The tapped density was calculated using the formula.

Tapped Density (T.D) = W / Vf

Angle of repose:

Angle of repose (*a*) was determined by using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (*h*) was obtained. The radius of the heap (*r*) was measured and angle of repose was calculated.

a = tan-1 (*h*/*r*)

Compressibility index:

The simplest way measurement of free flow property of powder is compressibility, an indication of ease with which a material can be induced to flow is given by % compressibility, which is calculated as follows:

C = [(T.D-B.D) / T.D] x 100

Where T.D and B.D are bulk density and tap density respectively.

Hausner's ratio:

Hausner's ratio is an index of ease of powder flow; it calculated as follows:

Hausner's ratio = T.D / B.D

Where T.D and B.D are bulk density and tap density respectively.

Evaluation of tablets:

All the tablets were evaluated for different parameters like hardness, thickness, friability, wetting time, drug content, disintegration time *in-vitro* drug Release and *In-Vivo* studies.

Hardness: For each formulation hardness was tested using the Pfizer hardness tester (Cadmach, India)

Friability:

Twenty tablets were weighed and placed in Roche friabilator (Electrolab, Mumbai) and apparatus was rotated at 25 rpm for 4 min. After revolution tablets were dusted and weighed [1, 2]. The friability is given by the formula:

F = [1- Wo / W] x 100

Where, Wo = weight of the tablets before the test, W = weight of the tablets after the test.

Drug content:

Finely powder not fewer than 20 tablets. Transfer a portion of the powder,equivalent to 50mg of tramadol hydrochloride, and transferred to a 100ml volumetric flask; the volume was made-up with 0.1 N HCl and sonicated for 30 min to break the complex. The samples were filtered through Whatman filter paper No. 41, diluted suitably and absorbance was measured at 272 nm.

Wetting Time

A Petri dish containing 6 ml of distilled water was used. A tissue paper

folded twice was kept in the dish and a tablet was placed on it. A small quantity of amaranth red color was put on the upper surface of the tablet. Time required for the upper surface of the tablet to become red was noted as the wetting time of the tablet

Disintegration time:

The in-vitro disintegration time was determined by using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds.

***In vitro* drug release**:

The *In vitro* dissolution test was carried out using USP Type II dissolution test apparatus at 37±2°C and 50 rpm speed. 900 ml of 0.1 N HCl was used as dissolution medium. Aliquot equal to 10 ml was withdrawn at specific time intervals and amount

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of Tramadol released from tablet was determined.

Release Kinetics

The results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows[5,6,7]

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchis model)
3. Cumulative percent drug release versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (korsmeyers model)

Stability Studies:

The purpose of stability testing 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 and light, and enables recommended storage conditions and shelf lives to be established. In the present study, the stability studies were carried out as per ICH guidelines 40°C ± 20°C / 75% ± 5% RH for the selected formulation F3 for 1 month. After specified time intervals, parameters like physical appearance, disintegration time, drug content, and dissolution were evaluated according to the procedure described as earlier.

In vivo Studies [8,9]

Healthy Adult rabbits were used for the study. (Approval number: IAEC/XXXIV/05/CLBMCP/2011 dated 07.12.2011). Physical examinations and plasma biochemical analyses were performed to ensure rabbits were healthy prior to the experiment. One blood sample was collected before treatment with tramadol through marginal ear vein. Then, tramadol was administered once, and blood samples were collected at various time points up to 6hrs after administration. Blood samples were analyzed with high performance liquid chromatography to determine plasma concentrations of tramadol.

Results and Discussion:

Table 2: Evaluation of precompressed granules of Tramadol HCL

Formulation	Bulk density (gm/cc) ± SD	Tapped density (gm/cc) ± SD	Compressibility index (%) ± SD	Hausner's ratio (%) ± SD	Angle of repose ( ) ± SD
F1	0.289±0.023	0.344±0.03	13.47±0.002	1.155±0.04	21.98±0.03
F2	0.309±0.021	0.348±0.012	11.02±0.03	1.126±0.01	20.43±0.04
F3	0.296±0.012	0.321±0.02	7.78±0.001	1.084±0.03	19.69±0.02
F4	0.293±0.023	0.316±0.023	7.27±0.012	1.078±0.01	20.79±0.05
F5	0.312±0.032	0.375±0.012	16.80±0.023	1.201±0.02	22.31±0.04
F6	0.295±0.014	0.342±0.021	13.74±0.023	1.159±0.31	21.01±0.21
F7	0.307±0.032	0.370±0.021	17.02±0.001	1.205±0.01	22.24±0.04
F8	0.281±0.041	0.324±0.012	13.27±0.001	1.153±0.02	19.76±0.03
F9	0.318±.021	0.347±0.024	8.35±0.002	1.091±0.03	21.47±0.05

Table 3: Evaluation of Compressed Granules of Tramadol HCL

Formulation	Weight Variation	Hardness (kg/cm2)	Thickness (mm)	Friability (%)
F1	299±0.14	3.48±0.12	3.62± 0.016	0.462
F2	305±0.25	5.65±0.11	3.14±0.012	0.501
F3	301±0.01	4.53±0.14	3.42±0.01	0.442
F4	305±0.43	3.51±0.12	4.14±0.14	0.364
F5	304±0.38	4.21±0.14	3.27±0.03	0.409
F6	302±0.24	4.04±0.15	4.01±0.02	0.486
F7	298±0.18	4.79±0.14	3.93±0.12	0.423
F8	304±0.16	4.23±0.16	3.76±0.01	0.412
F9	306±0.41	4.54±0.13	4.15±0.13	0.389

Table 4: Evaluation of Compressed Granules of Tramadol HCL

Formulation	Wetting Time (sec)	Disintegrating Time (sec)	Drug content (%)
F1	75	31	98.23
F2	41	24	98.76
F3	23	18	99.12
F4	29	20	101.76
F5	30	27	100.14
F6	35	29	98.99
F7	29	32	99.01
F8	31	27	98.66
F9	27	26	98.41

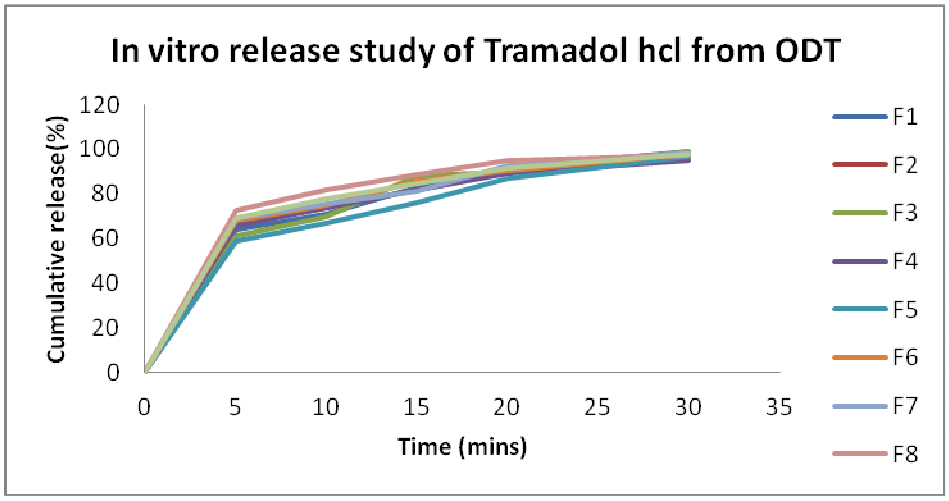

Figure 1: *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F1-F9)

Determination of Release Kinetics:

Table 5: Kinetic Studies of Oral Dispersible Tablets

Release kinetics	R^2	Intercept	Slope
Zero order	0.971	54.48	1.573
First order	0.908	2.142	0.067
Higuchi	0.982	32.33	12.31
Korsmeyer peppas	0.972	1.577	0.280

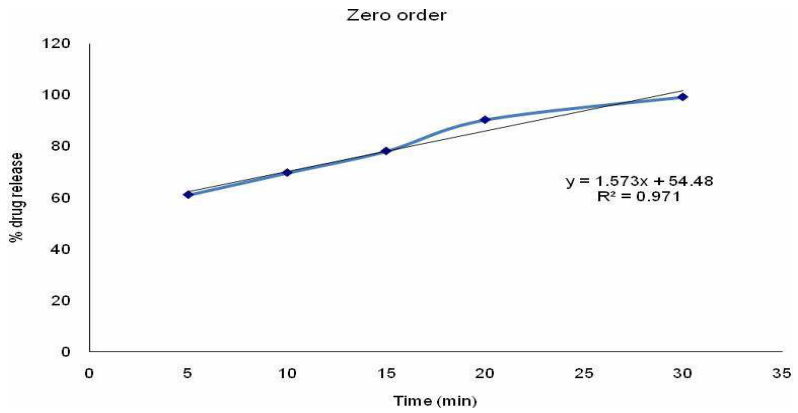

Fig. 2: Graph for the Formulation F3-Zero Order Kinetics

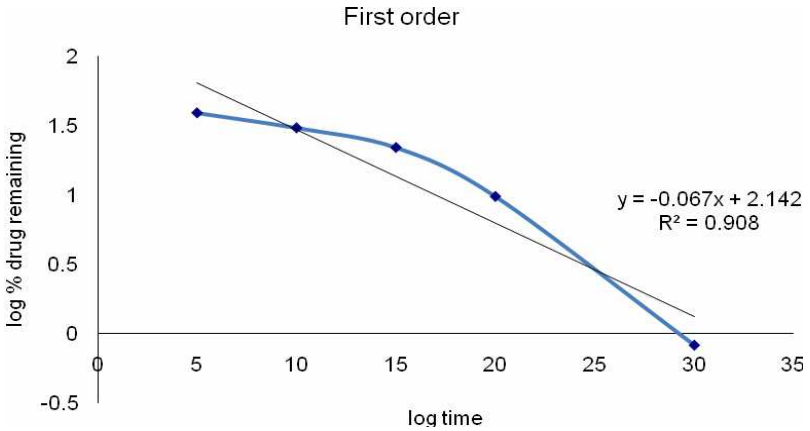

Fig. 3: Graph for the Formulation F3-first Order Kinetics

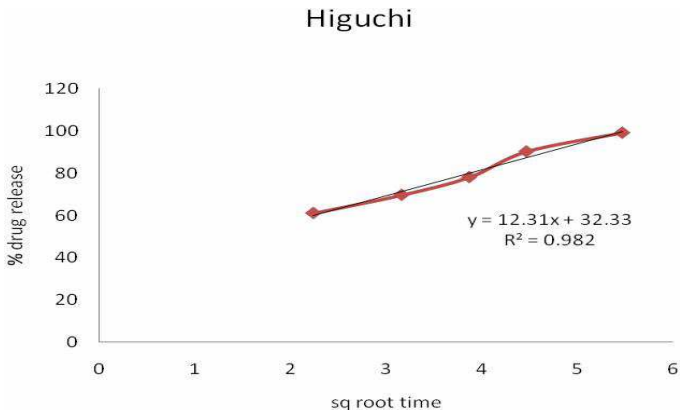

Fig. 4: Graph for the Formulation F3-higuchi model

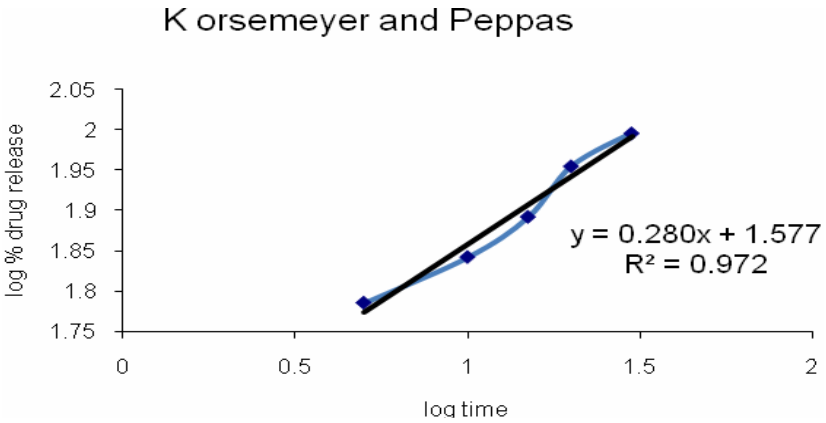

Fig. 5: Graph for the Formulation F3-Korsmeyer-Peppas model

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Stability Studies

Table 6: Stability Studies for F3 Formulation of Tramadol Hydrochloride ODT at 40° C /75 %RH

Batch number and stability condition	Assay (%)	Dissolution study in pH 1.2 buffer	Friability (%)	Hardness (kg/cm²)	Disintegration time (sec)
40° C/75 % RH (Initial)	99.12%	99.18±0.16%	0.442	4.53±0.14	18
40° C/75 % RH (15 days)	99.64%	99.14±0.32%	0.482	4.49±0.10	18
40° C/75 % RH (1 month)	99.64%	99.76±0.12%	0.469	4.55±0.12	19

In-Vivo release study

invivo pharmacokinetic parameters for Tramadol hydrochloride (F3)

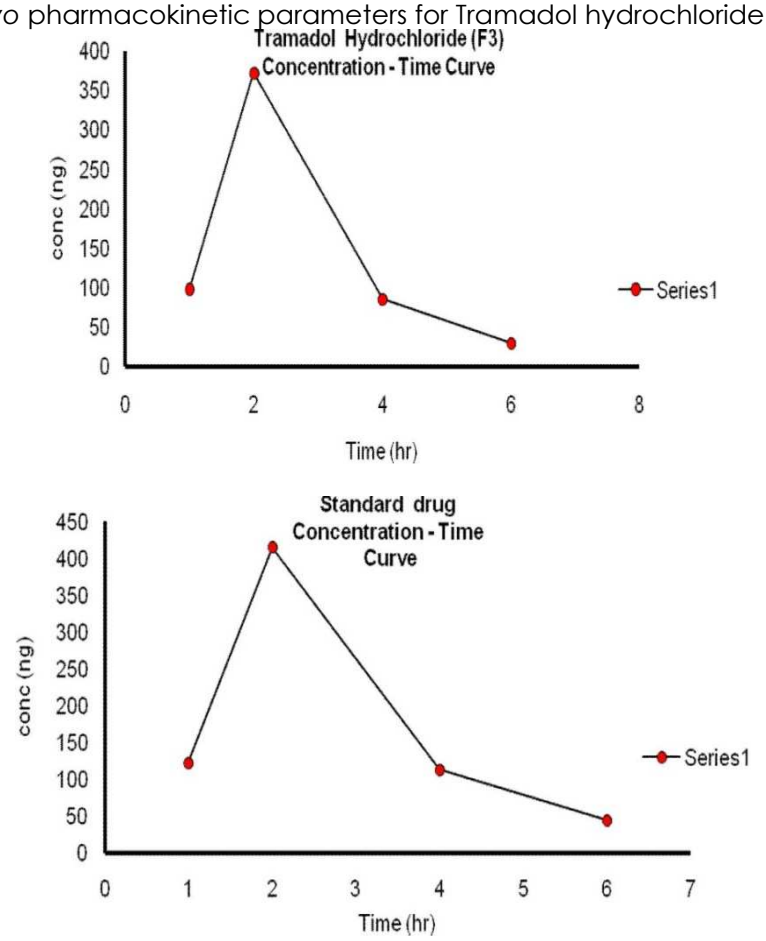

Fig. 6: *invivo* Pharmacokinetic Parameters for Tramadol hcl(A) and Marketed Product(B)

Table 7: Pharmacokinetic Parameters of Tramadol Hcl and Marketed Product

Parameters	Tramadol Hcl	Marketed formulation
Cmax	371.5	414.6
Tmax	2.0	2.0
AUC(0-t)	857.5 ng-hr/ml	1014.2 ng-hr/ml
$AUC_{(\infty)}$	915.2 ng-hr/ml	1110.8 ng-hr/ml
$AUMC_{(\infty)}$	2536.8 ng-hr*hr/ml	3325.1 ng-hr*hr/ml
E Phase	695.112	716.463
D/A Phase	772.892	830.576
MRT (area)	2.8 hr	3.0 hr

Discussion

Tramadol Oral Dispersible Tablets were prepared using different percentages of Crospovidone, Croscarmellose sodium and SSG as superdisintegrants by direct-compression method.The granules prepared using Crospovidone, Croscarmellose sodium and SSG as superdisintegrants for compression of orally disintegrating tablets were evaluated. the prepared granules exhibited good flow properties. The results were shown in **Table 2.**

On immersion in 0.1M HCl, pH 1.2 solution at 37±0.5^0 c all oral dispersible tablets remained buoyant up to 30 min. Crosspovidone due to their non-ionic nature, pyrolidone chemistry and porous particle morphology, will rapidly absorb water via capillary action. Other super disintegrants, like sodium starch glycolate and croscarmallose sodium have lower crosslink density and as a result, form gels when fully hydrated, particularly at higher use.F3 with 4% crospovidone had better dissolution properties. Stability studies were conducted for the formulation F3. The stability study was performed at 40^0 C±2^0 C/75% RH for a specific period of time.. The overall results showed that the formulation is stable at the above mentioned storage conditions shown in **Table 6 .** *In vivo* studies were done to find out the pharmacokinetic parameters of the optimized formulation with the market product.The Cmax for the innovator product was found to be 414.58ng/ml and for the Tramadol hydrochloride (F3) was found to be 371.51ng/ml. The Tmax of the innovator product and Tramadol hydrochloride (F3) shows at 2nd hour. $AUC_{(0-t)}$ for the innovator product and Tramadol HCl (F3) was 1014.2 ng-hr/ml & 8575.5 ng-hr/ml. AUMC) shows 332.1 ng-hr*hr/ml & 2536.8 ng-hr*hr/ml for innovator product and Tramadol HCl.

Conclusion

The formulation containing 50mg of Tramadol hydrochloride was prepared as orally dispersible tablet. These techniques are particularly useful for geriatrics and pediatrics as it can be taken without the aid of water.The optimized formulation have consistent release profile to provide the disintegration with in one minute by Crospovidone (F3).The short term stability study also indicates no change in the physical characteristic of drug content.The comparision of pharmacokinetic parameters between the ODTs Tramadol HCl and conventional tablet, showed no major changes in the pharmacokinetic parameters. Hence, it can be concluded that the ODTs of Tramadol HCl was successfully developed and evaluated.

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