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Design and Evaluation of Fast Dissolving Tablets of Fexofenadine by Using Novel Super Disintegrants

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A B S T R A C T

The purpose of this research was to formulate tasteless complexes of Fexofenadine Hydrochloride with Amberlite IRP-64 and to formulate tasteless complex into Orally-Disintegrant tablets (ODT) for the treatment of allergic rhinitis & chronic idiopathic urticaria. Tasteless Drug resin complexes (DRC) were prepared using combination of Amberlite IRP-64 & drug in different ratio (1:1, 1:2 & 1:3) and evaluated for different factor affecting Drug-Resin Complexation, Complexation time, stirring time, soaking time, temperature, and effect of pH on Fexofenadine Hydrochloride loading on Amberlite IRP-64.The values of precompression parameters evaluated, were within prescribed limits and indicated good free flowing properties. The tablets were evaluated for post-compression parameters such as weight variation, hardness, and friability, wetting time, content uniformity, disintegration time and dissolution. The study conclusively demonstrated significant taste masking of API and rapidly dispersible and dissolution. Maximum loading was obtained at drug–resin ratio 1:1, pH 6-7, temperature 60 ºC, soaking time 60 min and stirring time 5-6 hr. Formulation F-9 containing Amberlite IRP-64 & CSS show optimum result among all formulation. Formulations F-9 was found to be palatable with in vitro disintegration time of 30s, dissolution studies showed complete release of F-9 within 30 min.

Keywords: Fexofenadine Hydrochloride, Fast-Disintegrating tablets (FDT), Amberlite IRP-64, *In-vitro* drug release

A R T I C L E I N F O

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1. Introduction

The concept of Fast dissolving Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult.

Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva [1-3]. The center for drug Evaluation and Research states an ODT to be: "A solid dosage form containing medicinal substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue."[4]

These tablets are distinguished from conventional, sublingual tablets, lozenges and buccal tablets which require more than a minute to dissolve in the mouth. In the literature these are also called orally disintegrating, Orodisperse, Mouth dissolving, quick dissolving, Fast-melt and rapidly disintegrating tablets and freeze- dried wafers [5-6].

Taste masking of bitter drugs is a big challenge to formulator in developing a drug product with good organoleptic properties for patient acceptance and compliance. Though there are several methods available for taste masking of bitter actives, a method that is gaining wider acceptance is use of ion exchange resins (IER). IER are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. However, the utility of ion exchange resins for taste masking is product specific and there are various factors like resin-type, loading method, particle size of resin and degree of cross linking of resin that influence formation of a resinate. Also, in recent times, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication [7].

A 'patient-friendly dosage form' improves patient acceptance and compliance. Major challenges to this are the bitter taste of drugs and dosage forms that are difficult to ingest, carry or store. Present work explores the potential of ion exchange resins for taste masking of bitter drug, Fexofenadine hydrochloride and formulating it in the form of an Orally Disintegrating Tablet, which is gaining popularity as a dosage form. Fexofenadine HCl (FXD), is a non-sedating anti histamine used in the symptomatic relief of allergic conditions including seasonal allergic rhinitis, urticaria and hay fever. Fexofenadine, like other second and third-generation antihistamines, does not readily pass through the blood-brain barrier, and so causes less drowsiness than first-generation histamine-receptor antagonists [8].

In the Present study an attempt has been made to mask the taste of Fexofenadine HCl and to formulate Fast Disintegrating tablet with good mouth feel so as to enhance the patient compliance.

2. Materials and Methods

Materials:

Fexofenadine hydrochloride was obtained as a gift sample from Dr. Reddy's laboratories, API Unit VI. Amberlite IRP 64 was obtained from *Rohm* & *Haas India Pvt, Ltd.*Sodium starch glycolate NF was obtained from DMV-Fonterra excipients. Microcrystalline cellulose from FMC International, Colloidal silicone dioxide NF from Evonik industries Degussa and Magnesium Stearate from Nitika Chemicals.

Chemical compatibility:

FTIR studies were done to verify if there was any interaction between the pure drug and excipients employed. The various FTIR graphs of pure drug, physical mixture and placebo are mixed and the blend was formulated into IR pellet and scanned.

Preparation of taste masked orally dispersible tablets of Fexofenadine HCl [9,10]

- Fexofenadine HCl and amberlite IRP-64 resin were co-sifted through 40 sieve. Avicel ph101, sodium starch glycolate, aerosil, straw berry flavour and magnesium stearate passed through 40 sieve and collected in poly bag.
- Fexofenadine drug and amberlite IRP-64 resin are dissolved in water and stirred on magnetic stirrer for specific period of time and allowed to complex each other to form a taste masked drug resin complex.
- Transfer the sifted material into the RMG and mixed for 15 minutes
- Sifted the dried granules of 2nd step through # 20 sieve and collect the oversized granules separately.
- Magnesium stearate was sifted through # 60 sieve, added to the blend and mixed for 5 minutes.
- Granules prepared from above process are subjected for Tablet making. Tablets were compressed using compression machine with lubricated blend, employing appropriate punch tooling. Collect the compressed Tablets in double poly lined bag.

Evaluation Parameters

Parameters related to Drug Resin Complex [11,12]

Selection of Resin: In the present work weak cation exchange resin i.e. Amberlite IRP-64 & Amberlite IRP-69 are used for the taste masking of Fexofenadine HCl. Weak cationic exchange resins are used here because of weak

binding capacity and basic nature of Fexofenadine HCl; therefore they were selected for the immediate release taste masking formulation. It was observed that stirring for 5 h is required to achieve drug loading equilibrium, hence all further samples were stirred for 5 hours.

Study of Drug-Resin ratios:

To study the effect of drug-resin ratios on rate and extent of drug loading on resin, three different ratios1:1, 2:1, 3:1 of drug-resin were selected .The experiment was carried out by using Amberlite® IRP-64 by single batch method.

Evaluation of Pre Compression Micromeritic Parameters [13, 14]

Micromeritic properties of granular blend were tested before compression. The parameters that were tested are bulk density, tapped density, carr's index, hausner's ratio and angle of repose.

Post compression parameters [13, 14]

Hardness test: The crushing strength (kg/cm^2) of tablets was determined by using Monsanto hardness tester.

Weight variation: Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation were calculated. The test for weight variation is passed only if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown, Result was shown in Table No. 2.

Table 1: Formulation formula

Ingredient	Quantity of ingredients								
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	F-6	**F-7**	**F-8**	**F-9**
Drug: resin complex (In %)	Eq.60 mg	Eq.60 Mg	Eq.60 Mg	Eq.60 Mg	Eq.60 Mg	Eq.60 Mg	Eq.60 Mg	Eq.60 Mg	Eq.60 Mg
Avicel PH102	25	23	21	25	23	21	21	21	21
SSG	2	4	6	----	----	----	4	2	3
CCS	----	----	----	2	4	6	2	4	3
Aerosil 200	1	1	1	1	1	1	1	1	1
Aspartame	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Strawberry flavour	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg	90 mg

Table 2: Weight variation requirements as per USP

Average weight	% Difference
130mg or less	10
More than 130mg to 324mg	7.5
More than 324mg	5

Friability: The friability values of the tablets were determined using a Roche friabilator. It is expressed in %.20 tablets were initially weighed (initial weight) and transferred to friabilator. Friabilator was operated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

$$\% \text{ Friability} = \frac{\text{Initial wt} - \text{Final wt}}{\text{Initial wt}} \times 100$$

Drug content:

For determination of drug content three tablets from each formulation were weighed individually, crushed and diluted to 100ml with sufficient amount of PH 7.4. Then aliquot of the filtrate was diluted suitably and analyzed spectro-photometrically at 223 nm against blank.

Taste Evaluation:

The taste characteristic of Fexofenadine HCl ODT formulations was compared in healthy human volunteers, from whom informed consent was first obtained. The evaluation was based on the extent to which subjects liked the taste of each ODT. Formulations were rated on a scale of 0 through 3. Where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness [15].

In vitro drug release of orally dispersed tablets

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium consisted of 900 ml of phosphate buffer pH 3, The release was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. Samples (5 ml) were withdrawn at 0, 5, 10, 15, 20, 25 & 30 min time intervals and replaced with fresh medium. The samples were filtered through filter paper and analyzed by UV spectrophotometer at 223 nm.

Stability Studies [16,17]

The design of the formal stability studies for the drug product was based on the knowledge of the behaviour and properties of the drug substance and formal stability studies on the drug substance. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH. The selected batch was kept at 40°C with 75% RH and the samples were withdrawn at 30, 60 and 90 days for physical and *in vitro* evaluation of drug release.

Table 4: Storage Conditions in Stability Studies

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C/60%RH	After 30 days
Intermediate	30°C/75% RH	After 30 days
Accelerated	40°C/75% RH	After 30 days

When significant change occurs at any time during 1 month testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria

3. Results and Discussion

Chemical Compatibility Studies:

Fourier transformer infrared spectroscopy

The FTIR spectra of pure Fexofenadine hydrochloride, amberlite IRP-64 physical mixtures with Fexofenadine hydrochloride are shown in Figure 1-4. The IR spectrum of pure drug and physical mixture of drug and polymer of optimized formulation were studied. The characteristic absorption peaks of Fexofenadine hydrochloride were obtained at 3367 cm^{-1}, 1716.53 cm^{-1}, 1446.51 cm^{-1}, & 1249.75 cm^{-1}. The peaks also obtained in the spectrum of each physical- mixtures of the optimized formulation. By correlating Fexofenadine hydrochloride peaks of pure drug spectrum with physical- mixtures of the optimized formulation it was found that the drug is compatible with the formulation components.

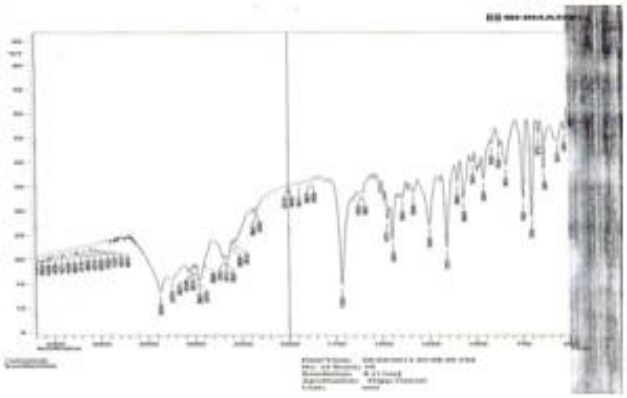

Figure 1: FT-IR Spectrum of Fexofenadine hydrochloride

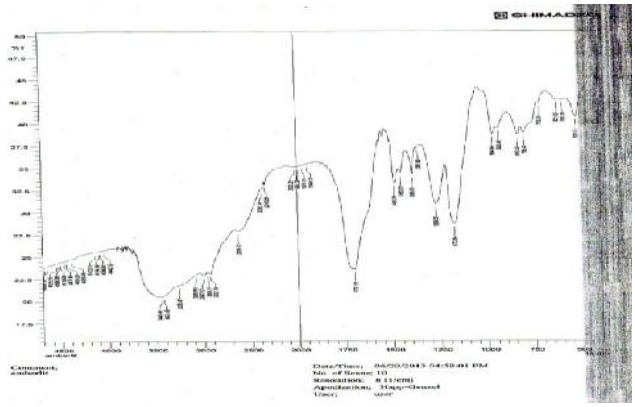

Figure 3: FT-IR Spectrum of Amberlite Resin

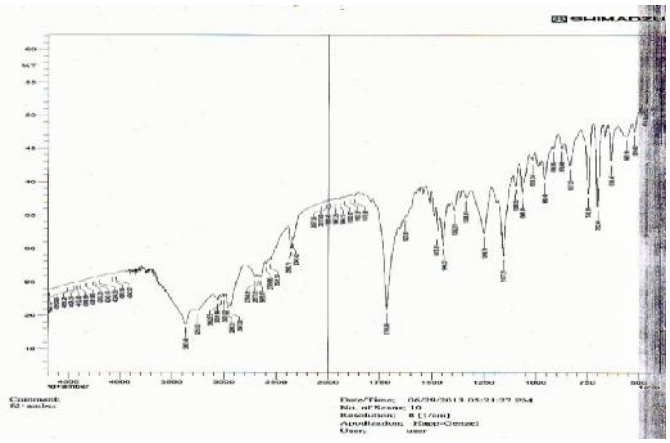

Figure 2: F T-IR Spectrum of Fexofenadine Hydrochloride + Amberlite

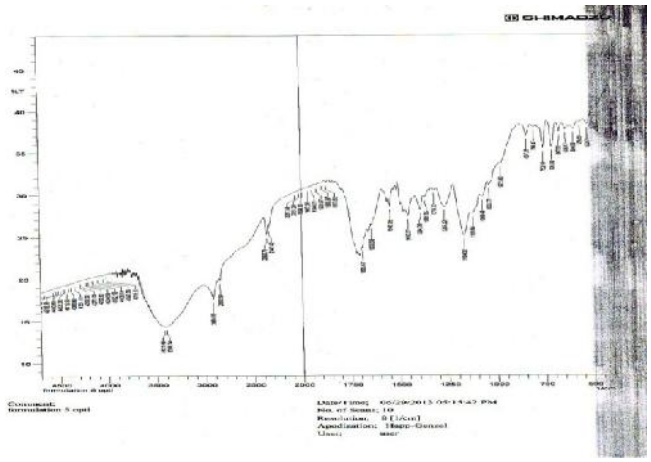

Figure 4: FT-IR Spectrum of Optimized Formulation

Evaluation of Pre Compression Parameters

Parameters Related to Drug resin complex

Selection of resin: The % amount of drug bound the resin after complexation in amberlite IRP-64 & 69 found to be 47.30 & 34.78 respectively, the highest % of drug complexation was observed in amberlite IRP-64, so it was selected as the complexing resin.

Table 5: Selection of ion exchange resin

Resin	Fexofenadine HCl : Amberlite IRP-4 ratio	% Fexofenadine HCl content of Resinate After 5hrs
Amberlite IRP-64	1:1	47.30
Amberlite IRP-69	1:1	34.78

Study of Drug-Resin ratios: The Amount of Fexofenadine HCl present in drug Resinate ratio of 1:1 was 47.30 % where the % of drug in 1:2 ratio is 37.57 %. The studied result show that Fexofenadine HCl: Amberlite IRP-64 (1: 1) ratio gives best loading was 90 % after 5 hrs and drug content of Resinate was 47.30 %.

Table 6: Selection of drug resin ratio

Fexofenadine HCl : Amberlite IRP-4 ratio	% Fexofenadine HCl content of Resinate After 5hrs
1: 1	47.30
1: 2	37.57

Micromeritic properties:

The angle of repose for the formulations was found to be in the range of 25.21±0.24^o to 30.18±0.34^o. The bulk density and tapped density for the formulations were in the range of 0.44±0.01- 0.46±0.014 & 0.54±0.032-0.57±0.061 gm/ml. Compressibility index and Hauser's ratio were in the range of 16.66±0.45to 20.0±0.25% and 1.20±0.16 to 1.24±0.21 respectively. From the above trial batches Formulations trials F1, F2, F3, F5, and F6 showed passable flow properties, whereas trials F7, F-8, and F9 showed good flow properties and trial F4 showed poor flow properties. The results obtained confirm that the batchF-9 which exhibit good flow properties have good packing characteristic.

Table 7: Evaluation of Pre Compression Micromeritic Parameters

Formulation Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose	Carr's index	Hausner's Ratio
F1	0.44±0.01	0.54±0.044	25.41±0.41	18.51±0.77	1.22±0.52
F2	0.44±0.021	0.55±0.028	27.05±0.21	20.0±0.25	1.25±0.16
F3	0.46±0.014	0.57±0.012	28.19±0.18	19.29±0.16	1.23±0.23
F4	0.45±0.019	0.55±0.023	25.21±0.24	18.18±0.17	1.22±0.14
F5	0.45±0.023	0.54±0.042	24.34±0.43	16.66±0.45	1.20±0.22
F6	0.46±0.015	0.57±0.061	27.20±0.24	19.29±0.57	1.23±0.18
F7	0.45±0.021	0.56±0.034	27.22±0.34	19.64±0.43	1.24±0.21
F8	0.46±0.017	0.56±0.044	28.34±0.32	17.85±0.61	1.21±0.31
F9	0.45±0.012	0.54±0.032	30.18±0.34	16.66±0.62	1.20±0.16

All the values are expressed as mean ± S.D; No. of trails (n) =9.

Evaluation of Post Compression Parameters:

Formulations trials F1, F4, F5, and F5 did not achieve required hardness, whereas trials F7 and F8 showed required hardness, friability, thickness. Trial (F9) is taken as optimized formulation batch, since all the parameters are found to be within limits when compared with all formulations.

Table 8: Evaluation of Post Compression Parameters

Test	Weight variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Wetting time (Seconds)	*In vitro* disintegration time (Seconds
F-1	90.3	4.2± 0.65	0.88	98.23 ± 0.59	120.67 ± 1.53	39.23 ± 0.53
F-2	89.8	4.1±0.28	0.85	97.56 ± 0.65	118.33 ± 1.15	45.47 ± 0.83
F-3	89.3	4.4±0.28	0.82	98.28 ± 0.35	112.67 ± 3.21	37.81 ± 1.23
F-4	90.4	4.2±0.19	0.84	95.8 ± 0.20	108 ± 1.00	42.95 ± 0.59
F-5	90	4.3±0.18	0.80	98.47 ± 0.56	96.56 ± 1.53	38.02 ± 1.58
F-6	90.7	4.5±0.15	0.79	99.90 ± 0.10	96.30 ± 2.00	36.24 ± 1.11
F-7	89.3	4.5±0.12	0.78	99.25 ± 0.18	97.25 ± 0.18	32.22 ± 0.86
F-8	90.4	4.7±0.16	0.76	95.25 ± 0.25	95.25 ± 0.18	36.43 ± 0.78
F-9	90.1	4.8±0.55	0.72	99.25 ± 0.15	95.22 ± 0.86	29.25 ± 0.95

All the values are expressed as mean ± S.D; No. of trails (n)=6

Taste Evaluation

Table 9: Evaluation of taste of the Formulated ODT

Form of Dextromethorphan HBr	Degree of bitterness after time			
	10 s	1 min	5 min	10 min
Pure drug	3	3	3	3
DRC	0	0	0.5	0
Formulated ODT	0+	0+	0+	0+

Results are the mean of 3 observations. + indicates palatability, DRC, Drug-Resin Complex.

Dissolution Profiles of Fexofenadine Hydrochloride Orally Dispersed Tablets:

We selected F9 as best formulation as it showed total drug release in 12hr as sustained manner than all other formulations.

Table 10: In-vitro dissolution profiles of the prepared formulations

Time (min)	Cumulative % drug release of formulation F1-F9								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	**0**
5	32.73	35.95	37.76	29.73	32.97	36.33	38.73	40.53	**42.15**
10	40.03	43.09	47.74	38.01	42.16	45.03	47.32	54.86	**53.35**
15	55.67	58.88	59.23	49.96	53.15	56.67	58.67	63.65	**64.07**
20	63.22	65.61	67.58	58.64	63.96	69.61	71.24	72.31	**76.67**
25	71.46	73.49	75.42	71.52	75.91	78.61	79.92	81.66	**85.16**
30	82.48	84.11	86.54	81.96	83.84	84.78	86.52	87.96	**94.73**

All the values are expressed as mean ± S.D; No. of trails (n) =6.

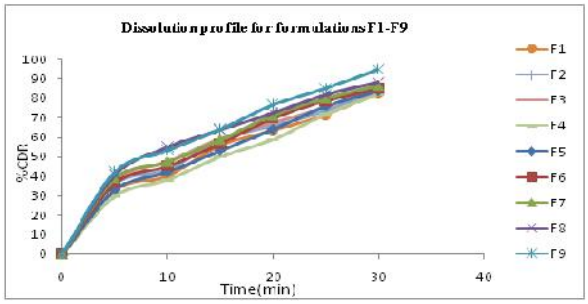

Figure 5: Dissolution profiles of F1-F8 formulations

Stability Study: There was no significant change in physical and chemical properties of the tablets of formulation F-9 after 30 days. Parameters quantified at various time intervals were shown.

Table 11: Stability dissolution profile of F-9 for 1st week, after 15 days and after 30days

S.No	Time (mins)	F-9 After 1week	F-9 After 15days	F-9 After 30days
1	0	0	0	0
2	5	41.50	40.82	40.10
3	10	52.25	52.15	52.09
4	15	63.27	63.07	62.81
5	20	74.55	74.39	74.20
6	25	85.25	84.16	83.02
7	30	94.63	94.61	94.58

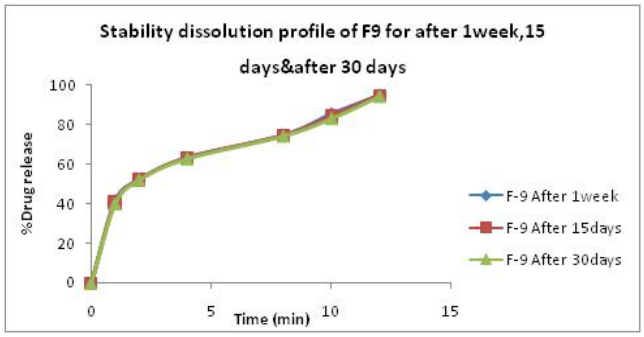

Figure 6: Dissolution profile of optimized batch after stability study

4. Conclusion

The fast disintegrant tablet is one of the best dosage form developed to overcome the difficulty in swallowing conventional tablets among pediatrics, geriatrics patients. From the preformulation studies it was found that, there was no interaction between drug- excipients combination. The standard formulations were prepared by using different super disintegrants with different ratio and found that, the results are within official limits with respect to weight, friability, disintegration time and assay. From the results obtained, the disintegration time and the In-vitro dissolution profile of formula 9 was good compared to other preparations. All the stability results were found to be satisfactory. Hence the designed and developed formula of Fexofenadine hydrochloride was stable. Fexofenadine hydrochloride Taste masked orally disintegrant tablets developed in the present work was found to be pharmaceutically better.

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