ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Mucoadhesive Potential of Whey Protein Concentrate in Miconazole Mucoadhesive Prolong Release Tablets

Khairnar Akshay*[1], Salunkhe Kishor[2], Chavan M J[1], Chintamani Ravindra[1]

[1]Department of Pharmaceutics, Amrutvahini College of Pharmacy, Sangamner, Ahmednagar -422608, Maharashtra, India

[2]Sanjivani College of Pharmaceutical Education and Research, Sahajanaandnagar, Shinganapur, Kopargaon, Ahmednagar-423603 , Maharashtra, India

Article History:

Received on: 21 Nov 2019
Revised on: 31 Jan 2020
Accepted on: 13 Dec 2019

Keywords:

Buccal Tablets, Hydroxypropyl methylcellulose, Miconazole, Whey Protein

ABSTRACT

Orophygial candidiasis (OPC) is one of the most frequent *Candida* infections of the oral cavity this condition is common in patients with malnutrition, having chemotherapy, administrating immunosuppressive agents, or severe disease such as HIV. Prolong local administration of Miconazole is a must to treat OPC conditions in patients, which required the prolong mucoadhesion of the dosage form to provide local delivery of drugs for an extended time period with good mucoadhesion. Miconazole is synthetic imidazole antifungal agent, various prescription and over the counter product available like Miconazole Gel, Topical cream, Immediate release Tablet available in the market but that lack in the prolonged period of action to the local mucosa. In the present study combination of Whey protein concentrate (WPC), Hydroxypropyl methylcellulose (HPMC) and Lactose were evaluated as a potential buccal adhesive tablet. The various combination of Whey protein concentrate with release controlling polymer was tested using a Miconazole as a potential antifungal agent. The mucoadhesive potential of WPC evaluated using Tensiometer by calculating the detachment force and drug release of Miconazole was performed to study the prolong release activity of Tablet. The optimized combination of WPC/HPMC/Lactose through a statistical study showed significant bioadhesion to the porcine mucosa and prolong drug release for 10hrs.

*Corresponding Author

Name: Khairnar Akshay
Phone: 91 9890424466
Email: akshaykhairnar@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i2.2006

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IJRPS | www.ijrps.com

INTRODUCTION

In recent years the effectiveness of formulation has been achieved through the controlled drug delivery platforms. Most of the work has been carried out in the area of bio adhesion, particularly the mucoadhesive drug delivery system, to improve the efficacy of drugs through oral, buccal, nasal route of administration (Patel *et al.*, 2011). Common polymers that have been used as mucoadhesive drugs carrier are polyethylene oxide (Roy *et al.*, 2009), Lecithin (Cook *et al.*, 2017), Chitosan, Polymethyl acrylates, Carbapol, Poly-carbophil, Sodium CMC (Rao *et al.*, 2013).

However, most of the polymers used in mucoadhesive drug delivery cause mucosal irritation limits its use in the therapeutic system (Ameye *et al.*, 2005).

In the present study, an attempt has been made to evaluate the potential of Whey protein concentrate as a mucoadhesive agent in combination with

Hydroxypropyl methylcellulose as release controlling agent (Biswas, 2016) for the Prolong delivery of Miconazole is an antifungal agent (Sawyer *et al.*, 1975).

Miconazole is a synthetic imidazole antifungal agent and most of the various prescription and over-the-counter products have been approved under various dosage forms like vaginal formulation (Kenechukwu *et al.*, 2018), dermal formulations, oral, gel, topical formulations which can be administered orally, intravenously and intrathecally.

Miconazole also indicated for the treatment of Orophygial candidiasis (OPC) one of the most frequent *Candida* infections of the oral cavity. If it is left untreated, it may invade the esophagus or further progress to induce systemic complications. This condition is common in patients with malnutrition, having chemotherapy, administrating immunosuppressive agents, or severe diseases such as HIV (Hermant *et al.*, 1997).

Prolong local administration of Miconazole is a must to treat OPC conditions in patients, which required the prolong mucoadhesion of the dosage form to provide local delivery of drugs for an extended time period with good mucoadhesion.

The Buccal administrations of drugs have gained interest as the oral cavity in disease conditions like OPC forms a convenient and easily accessible site for local and systemic delivery of the drug.

The present invention provides a carrier system with whey protein concentrate as a mucoadhesive agent to provide prolonged release bioadhesive therapeutic system that is essential for producing a long residence time in the locations of the infection in contrast to the usual local forms (mouthwashes, gel, pistils, lozenges) which have a transitional effect (Sarah *et al.*, 2019).

The Whey protein concentrate in combination with hydroxypropyl methylcellulose (HPMC) as a release controlling agent and Lactose monohydrate as a diluent come pore former have been evaluated in the present study as potential buccal bioadhesive tablets. The objective was to investigate the mucoadhesive potential of Whey protein concentrate in various combinations with release controlling polymer.

The bioadhesive strength of the WPC investigated and drug release characteristics evaluated with Miconazole as a potential antifungal drug.

The final combination of the polymer was optimized through the design of experiments using Mini Tab.

MATERIALS AND METHODS

Miconazole API received from Gufic biosciences as a gift sample, Whey protein concentrate (WPC) purchased from NZMP, Hydroxypropyl methylcellulose (Methocel K15 LV) from Colorcon Ltd, Lactose monohydrate 450M from Armor Pharma, Microcrystalline cellulose (Avicel PH 102) from FMC, Colloidal silicon dioxide (Roqquete), Magnesium stearate (Merck), Talc (Merck)

Preparation of the Buccal Tablets

After some preliminary trials, the following excipients were finalize for the preparation of tablets, wherein Miconazole dose kept as 50mg and tablet weight finalized as 115mg. The list of ingredients listed in Table 1.

The various combination of WPC, HPMC and Lactose have been performed through the design of experiments (DOE) full factorial design.

The selection of design is based on the impacts of the factor for that full factorial design is chosen with three center points. Design details are as below mention Table 2 and the design of trials in Table 3
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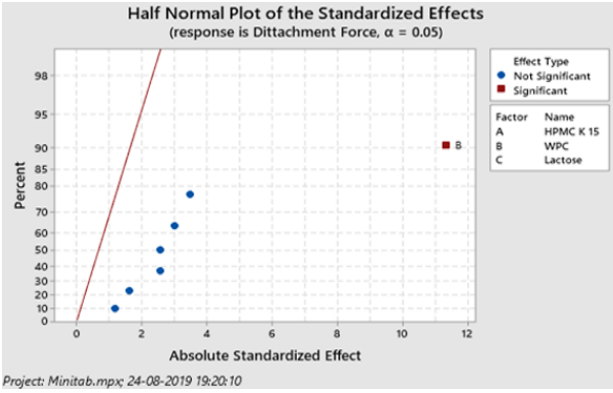

Figure 1: Half Normal Plot of detachment force

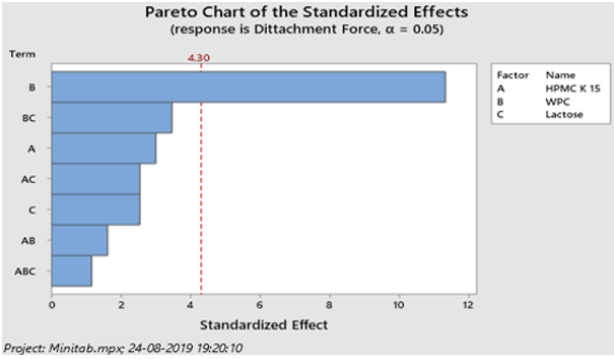

Figure 2: Pareto Chart of Detachment Force

Table 1: List of ingredient

S.No	Ingredient	Functionality
1	Miconazole	Active Pharmaceutical ingredient
2	Whey protein concentrate (WPC)	Mucoadhesive agent
3	Hydroxy propyl methyl cellulose (HYpromellose HPMC K15LV)	Release controlling polymer
4	Lactose Monohydrate (450M)	Diluent/Pore former
5	Microcrystalline cellulose (Avicel PH 102)	Diluent
6	Talc	Glidant
7	Magnesium stearate	Lubricant

Table 2: Design details of factors

Factors	3		Base Design	3, 8
Runs	11		Replicates	1
Blocks	1		Centre pts (total)	3
	Factors		Responses	
Factors	Level		Responses	Target
HPMC K 15	18	22	Detachment Force	Maximum
WPC	28	32	Dissolution at 3 Hr.	30 ± 10
Lactose	6	10	Dissolution at 6 Hr.	65 ± 10
			Dissolution at 8 Hr	At least 80 %

Table 3: Design of trials (run)

Std Order	Run Order	Factors (mg/tablet)		
		HPMC K 15LV	WPC	Lactose
1	1	18	28	6
2	2	22	28	6
3	3	18	32	6
4	4	22	32	6
5	5	18	28	10
6	6	22	28	10
7	7	18	32	10
8	8	22	32	10
9	9	20	30	8
10	10	20	30	8
11	11	20	30	8

Manufacturing process

Miconazole, Whey protein concentrate (WPC), Hydroxypropyl methylcellulose (Hypromellose HPMC K15LV), Lactose Monohydrate (450M) mixed and granulated using purified water in High shear mixture granulator (HSMG) followed by drying, Milling and milled granules were lubricated with Microcrystalline cellulose (Avicel PH 102) 11mg/tablet or adjusted quantity, talc (1mg/tablet) and Magnesium stearate (1mg/tablet).

Tablet weight kept as 115mg and weight compensation done with Microcrystalline cellulose (Avicel PH102)

Compression of the tablets performed using Tablet compression machine (Cad Mach Single rotory 8 Station) with specially designed 8 mm tooling having concave at one side and flat at other.

The compression force was kept in the range of 6-8KP.

Evaluation/Characterization

Determination of physical parameters of tablets

Table 4: Bioadhesion and Drug release

Std Order	Run Order	Factors			Response			
		HPMC K 15	WPC	Lac-tose	Detachment Force	Disso at 3 Hr	Disso at 6 Hr	Disso at 8 Hr
1	1	18	28	6	4.8	38	70	95
2	2	22	28	6	4.5	26	53	80
3	3	18	32	6	6.7	35	74	95
4	4	22	32	6	5.8	22	51	79
5	5	18	28	10	5.3	32	71	90
6	6	22	28	10	5.3	32	58	92
7	7	18	32	10	6.2	35	74	93
8	8	22	32	10	6.1	29	64	82
9	9	20	30	8	6.5	28	55	86
10	10	20	30	8	6.7	32	58	90
11	11	20	30	8	6.8	29	62	88

Table 5: Factorial Regression: Detachment Force versus HPMC K15, WPC, Lactose, Centre Pt

S	R-sq	R-sq(adj)	R-sq(pred)
0.152753	99.28%	96.40%	*

Table 6: Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	8	6.42970	0.80371	34.44	0.029
Linear	3	3.36375	1.12125	48.05	0.020
HPMC K 15	1	0.21125	0.21125	9.05	0.095
WPC	1	3.00125	3.00125	128.62	0.008
Lactose	1	0.15125	0.15125	6.48	0.126
2-Way Interactions	3	0.49375	0.16458	7.05	0.127
HPMC K 15*WPC	1	0.06125	0.06125	2.63	0.247
HPMC K 15*Lactose	1	0.15125	0.15125	6.48	0.126
WPC*Lactose	1	0.28125	0.28125	12.05	0.074
3-Way Interactions	1	0.03125	0.03125	1.34	0.367
HPMC K 15*WPC*Lactose	1	0.03125	0.03125	1.34	0.367
Curvature	1	2.54095	2.54095	108.90	0.009
Error	2	0.04667	0.02333		
Total	10	6.47636			

Table 7: Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
2.08167	95.80%	78.98%	*

Table 8: Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	8	197.515	24.689	5.70	0.158
Linear	3	132.375	44.125	10.18	0.091
HPMC K 15	1	120.125	120.125	27.72	0.034
WPC	1	6.125	6.125	1.41	0.357
Lactose	1	6.125	6.125	1.41	0.357
2-Way Interactions	3	57.375	19.125	4.41	0.190
HPMC K 15*WPC	1	6.125	6.125	1.41	0.357
HPMC K 15*Lactose	1	45.125	45.125	10.41	0.084
WPC*Lactose	1	6.125	6.125	1.41	0.357
3-Way Interactions	1	3.125	3.125	0.72	0.485
HPMC K 15*WPC*Lactose	1	3.125	3.125	0.72	0.485
Curvature	1	4.640	4.640	1.07	0.409
Error	2	8.667	4.333		
Total	10	206.182			

Regression Equation in Uncoded Units

Disso at 3 Hr = 471 - 18.9 HPMC K 15 - 10.3 WPC - 64.9 Lactose + 0.406 HPMC K 15*WPC + 2.94 HPMC K 15*Lactose + 1.78 WPC*Lactose - 0.0781 HPMC K 15*WPC*Lactose - 1.46 Ct Pt

Table 9: Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
3.51188	96.55%	82.73%	*

Table 10: Regression Equation in Uncoded Units

Disso at 6 Hr	=	-481 + 28.4 HPMC K 15 + 23.3 WPC + 68.4 Lactose - 1.22 HPMC K 15*WPC - 3.69 HPMC K 15*Lactose - 2.59 WPC*Lactose + 0.141 HPMC K 15*WPC*Lactose - 6.04 Ct Pt

Table 11: Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
2	97.59%	87.94%	*

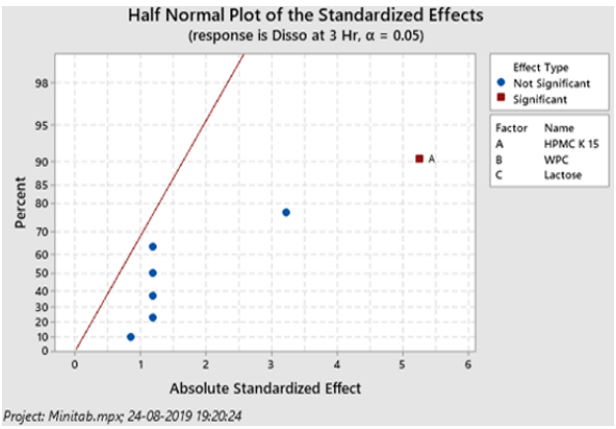

Figure 3: Half Normal plot

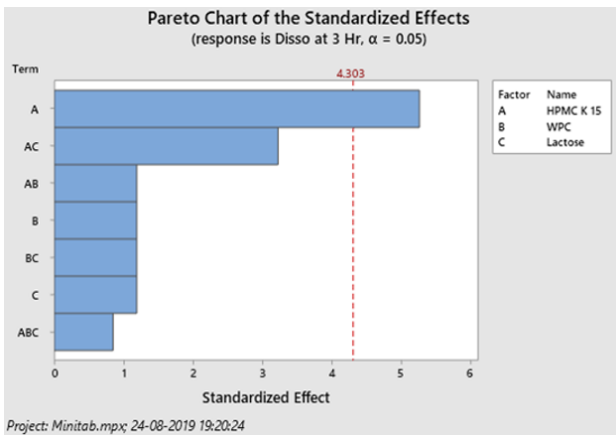

Figure 4: Pareto Chart

Table 12: Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	8	323.636	40.455	10.11	0.093
Linear	3	216.000	72.000	18.00	0.053
HPMC K 15	1	200.000	200.000	50.00	0.019
WPC	1	8.000	8.000	2.00	0.293
Lactose	1	8.000	8.000	2.00	0.293
2-Way Interactions	3	89.500	29.833	7.46	0.121
HPMC K 15*WPC	1	24.500	24.500	6.12	0.132
HPMC K 15*Lactose	1	60.500	60.500	15.13	0.060
WPC*Lactose	1	4.500	4.500	1.13	0.400
3-Way Interactions	1	18.000	18.000	4.50	0.168
HPMC K 15*WPC*Lactose	1	18.000	18.000	4.50	0.168
Curvature	1	0.136	0.136	0.03	0.871
Error	2	8.000	4.000		
Total	10	331.636			

Regression Equation in Uncoded Units

Disso at 8 Hr = 852 - 39.9 HPMC K 15 - 20.3 WPC - 120.1 Lactose + 1.063 HPMC K 15*WPC + 6.31 HPMC K 15*Lactose + 3.56 WPC*Lactose - 0.1875 HPMC K 15*WPC*Lactose - 0.25 Ct Pt

Table 13: Parameters for Optimization

Response	Goal	Lower	Target	Upper	Weight	Importance
Disso at 8 Hr	Target	79.0	80.0	95	1	1
Disso at 6 Hr	Maximum	51.0	74.0		1	1
Disso at 3 Hr	Maximum	22.0	38.0		1	1
Detachment Force	Maximum	4.5	6.8		1	1

Table 14: Solution for optimization

Solution	HPMC K 15	WPC	Lactose	Disso at 8 Hr Fit	Disso at 6 Hr Fit	Disso at 3 Hr Fit	Detachment Force Fit
1	22	32	10	82	64	29	6.1

Table 15: Multiple Response Prediction

Variable	Setting			
HPMC K 15	22			
WPC	32			
Lactose	10			
Response	Fit	SE Fit	95% CI	95% PI
Disso at 8 Hr	82.00	2.00	(73.39, 90.61)	(69.83, 94.17)
Disso at 6 Hr	64.00	3.51	(48.89, 79.11)	(42.63, 85.37)
Disso at 3 Hr	29.00	2.08	(20.04, 37.96)	(16.33, 41.67)
Detachment Force	6.100	0.153	(5.443, 6.757)	(5.171, 7.029)

Table 16: Actual Trial Results

Solution	HPMC K 15	WPC	Lactose	Disso at 8 Hr Fit	Disso at 6 Hr Fit	Disso at 3 Hr Fit	Detachment Force Fit
1	22	32	10	80	65	39	6

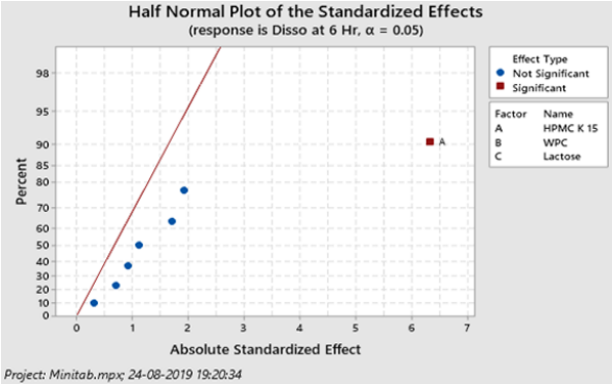

Figure 5: Half Normal Plot

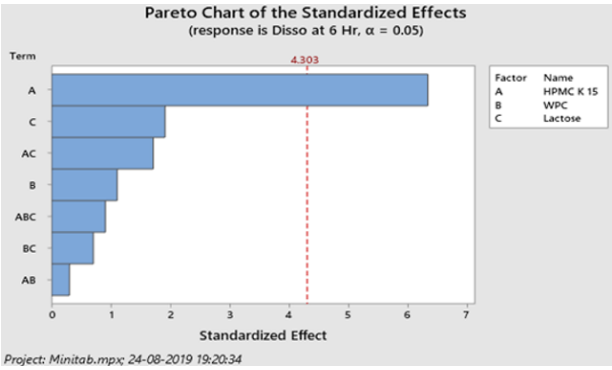

Figure 6: Pareto Chart

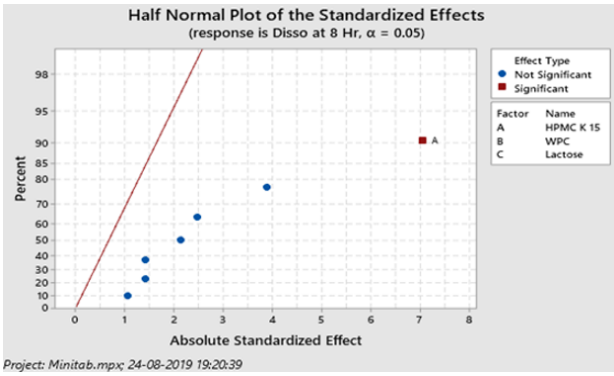

Figure 7: Half Normal Plot

Tablet thickness, Hardness, weight variation, friability test (www.usp.org ›document ›gen-chapter) performed as per USP and recorded.

Ex- Vivo determination of bio adhesion

In Vitro comparative bio adhesion study (peak detachment force) through Tensiometer (Jackson, 2001).

Porcine gingiva was obtained from slaughterhouse the mucosPO4,8.0g NaCl a were stored at−20 °C in isotonic buffered saline pH 7.4 (2.38 g Na2HPO4·H2O, 0.19 g KH2PO4,8.0g) NaCl made up to 1000 ml with demineralized water. The porcine gingival tissue was attached with glue to the plate of the tensiometer. After hydrating the mucosa with 15_l of the isotonic phosphate-buffered saline, the tablet was fixed on the mucosa applying a force of 0.5N for 5 min. After the initial contact, the thermostatic beaker (37 °C) was filled with 125 ml isotonic buffered saline pH 7.4 at 37 °C. Next, the tablet and mucosa were pulled apart at a speed of 5mmmin−1 until a complete ru and detachment force was recorded listed in Table 4.

Drug Release studies

Dissolution of all tablets was performed at the following condition (www.accessdata.fda.gov).

Apparatus USP I Basket, RPM 50, Medium pH 6.5 phosphate buffer with 0.5 % Sodium Lauryl Sulphate, Volume 1000mL,Time points 1Hrs, 3Hrs, 4Hrs, 6Hrs, 8Hrs and 10hrs. Results of the same shown in Table 4.

RESULTS AND DISCUSSION

Physical parameters of Tablets

Thickness: Avg : 2.2mm (n:12), Hardness : 3.1kp (n:12) ,Weight: 115.3 (n:12), Friability 0.06 %

Interpretation

From the above plots half-normal plot, Pareto chart and Interaction plot, it can be depicting that WPC is the most impacting factor on the Detachment force. As the concentration of the WPC increase, then Detachment force is also increasing Tables 5 and 6, Figure 1 and Figure 2.

Dissolution at 3hrs

Impact of dissolution at 3hrs shown in Tables 7 and 8, Figure 3and Figure 4.

Interpretation

From the above plots half-normal plot, Pareto chart and Interaction plot, it can be depicting that HPMC K 15 is the most impacting factor on Dissolution at 3 Hr. As the concentration of the HPMC increase, then Dissolution is also increasing.

Dissolution at 6 Hr

Impact of dissolution at 6hrs shown in Tables 9 and 10, Figure 5and Figure 6.

Interpretation

From the above plots half-normal plot, Pareto chart and Interaction plot, it can be depicting that HPMC K 15 is the most impacting factor on Dissolution at 6 Hr. As the concentration of the HPMC increase, then Dissolution is also increasing.

Response

Dissolution at 8 Hr

Impact of dissolution at 6hrs shown in Tables 11 and 12, Figure 7.

Interpretation

From the above plots half-normal plot, Pareto chart and Interaction plot, it can be depicting that HPMC K 15 is the most impacting factor on Dissolution at 8 Hr. As the concentration of the HPMC increase then Dissolution is also increasing.

Optimization

Optimized parameters were shown in Tables 13, 14, 15 and 16.

Inference

Above mention Trail was conducted for optimization predicted results and actual results are well within the limit. Hence it can be said that the product is optimized from above setting parameters with 95% CI.

CONCLUSIONS

The mucoadhesive potential of Whey protein concentrate has been investigated using Miconazole as a Model antifungal drug through the various combination with HPMC K15LV as a release controlling polymer. The optimized quantity of Whey protein 32mg/tablet) found to be providing good bioadhesive/mucoadhesive strength calculated using a tensiometer. The prolonged-release of Miconazole was obtained and an optimized combination of Whey protein, HPMC and Lactose have been established, which can be used as a platform technology for mucoadhesive drug delivery.

ACKNOWLEDGEMENT

Mr. Mandar Kor for supporting in statistical evaluation of data.

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