International Journal of Pharmaceutical and Life Sciences
ISSN 2305-0330
Volume 3, Issue 1: February 2022

IMPACT OF DIFFERENT EXCIPIENTS ON DISSOLUTION IMPROVEMENT OF LORATADINE BY SOLID DISPERSION

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Abstract
Loratadine is one of the most commonly used anti-histamine. It is practically insoluble in water. The onset of the action of the Loratadine is delayed due to its poor aqueous solubility. Now a days, solid dispersion is an emerging technology in the pharmaceutical industry to increase the solubility of poorly soluble drug by using different polymer/ excipients. In this study, Peg 6000, Poloxomer 188 & 407, HPC, HPMC, Crospovidone, Croscarmellose and Kollicoat IR were used to formulate solid dispersion of Loratadine. In case of HPMC formulations, significant % release of drug was observed within 10 minutes. With the increase of HPMC from 71% to 83%, release was increased from 61.86% to 71.88% after 60 minutes. HPMC based solid dispersion formulation can be a way to improve dissolution of loratadine in commercial production.

Keywords: *Loratadine, Solid Dispersion, Dissolution Improvement*

Introduction
The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is comfortable and a familiar means of taking medicine. Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via oral route. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membrane of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption[1]. In this article, dissolution improvement of poor aqueous soluble drug (Loratadine) has been discussed.

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Loratadine is a second-generation histamine H1 receptor antagonist which is used in the treatment of allergic rhinitis and urticaria. Unlike most classical antihistamines (histamine H1 antagonists) it lacks central nervous system depressing effects such as drowsiness[2]. Similar to other H1-blockers, Loratadine competes with free histamine for binding at H1-receptors in the gastrointestinal tract, uterus, large blood vessels, and bronchial muscle. Loratadine also has a weak affinity for acetylcholine and alpha-adrenergic receptors. Loratadine is practically insoluble in water. To improve the dissolution of Loratadine, solid dispersion technique has been used.

The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. It may be defined as the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method[3]. In practice, these dosage forms have been traditionally regarded as being synonymous with systems whereby the in-vitro release of the drug is enhanced compared to conventional dosage forms, with concomitant implications for in-vivo release. Furthermore, the carrier used has, again traditionally, been a water-soluble or water-miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as sugars. However, the proliferation of publications in the area since the first solid dispersions were described[4] has led to a broadening of these definitions to include water insoluble matrices such as Gelucires and Eudragits that may yield either slow or rapid release or absorption.

Materials and Methods

Materials Used

Table 1: List of Materials Used

Types	Name of the Materials	Source of the Materials
Drugs	Loratadine	Beximco Pharmaceuticals Ltd.
Solvents	Methanol	MERCK, Germany
	DI (Deionized) water	University Laboratory
	HPMC $_{5cp}$	BASF
	HPC	BASF

Table 1: List of Materials Used

Types	Name of the Materials	Source of the Materials
Polymers	Kollicoat IR	BASF
	Poloxomer 188	BASF
	Poloxomer 407	BASF
	Peg 6000	BASF
	Cross Povidone	BASF
	Cross Caramellose Na	BASF
	Lactose	Mingel, Germany

Equipment Used

Table 2: List of Equipment Used

USP Type III Dissolution Apparatus	VEEGO,India
UV –VIS Spectrophotometer (UVmini-1240)	SHIMADZU,Kyoto, Japan.
Electronic Balance (AY120)	SHIMADZU CORP., Japan.
Sonicator (Power Sonic 505)	HWASHIN TECHNOLOGY CO., Seoul, Korea.
Vortex Mixer (VM-2000)	Digisystem laboratory Instrument Inc., Taiwan.
Sieve 40 Mesh (Endecott's Test Sieve)	Endecotts Limited, England.
Hair Dryer	Commercially available in Bangladesh market

Preparation of Solid Dispersion

The method of preparation of solid dispersions was based on the “solvent evaporation method”. The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature[5]. The method has been described below:

In the solvent evaporation method of preparation, the carrier and the active ingredient are dissolved in the solvent (methanol) and the solvent is evaporated by a dryer (hair dryer). As the solvent is being removed, supersaturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue.

While preparing the solid dispersion of Loratadine, the drug solution was prepared by using drug, solvent (methanol) and polymer (HPMC 5cp, HPC, Peg 6000, Cross Povidone, Cross Caramellose, Poloxomer 188, Poloxomer 407, Kollicoat IR).

At first Loratadine (100 mg) was weighed accurately in an analytical balance and taken into dry and clean glass vials. Then each polymer was taken in the vial. Then methanol (4 ml) was added on each vial. Then drug and polymers were dissolved in methanol by sonication (5 minutes), vortexing (5 minutes) and then heating (at 50-60^{o}C for 5 minutes). Drug, polymer and solvent combination was dried by using hair dryer until solid dispersion was formed. The solvent evaporated completely. Finally, the formulations were withdrawn from vials, crushed by mortar & pestle and 1 gm lactose was added in each vial, then passed through sieve (40 Mesh). Then the resulted samples were weighed and transferred in fresh vials with proper labeling. Formulations were kept in desiccator until the dissolution started.

Preparation of Standard Curve for Loratadine

To prepare a standard curve of Loratadine, 20 mg of Loratadine was accurately weighed & dissolved in 1000 ml of 0.1 N HCl to produce a solution 20 µgm/ml. Then 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ml of this solution was taken in 10 ml volumetric flask and 9, 8, 7, 6, 5, 4, 3, 2, 1, 0 ml 0.1 N HCl was added to them for the purpose of serial dilution. This serial dilution was carried out to get different Loratadine concentration. These were then analyzed by UV spectrophotometer at 280 nm and absorbances were noted. Then absorbance values were plotted against drug concentration and standard curve of Loratadine was prepared.

Table 3 Absorbance values of the standard solution of Loratadine for Standard curve using 0.1 N HCl

Concentration (µgm/ml)	Absorbance
0	0
2	0.054
4	0.102
6	0.147
8	0.195
10	0.245
12	0.290
14	0.337
16	0.391
18	0.440
20	0.488

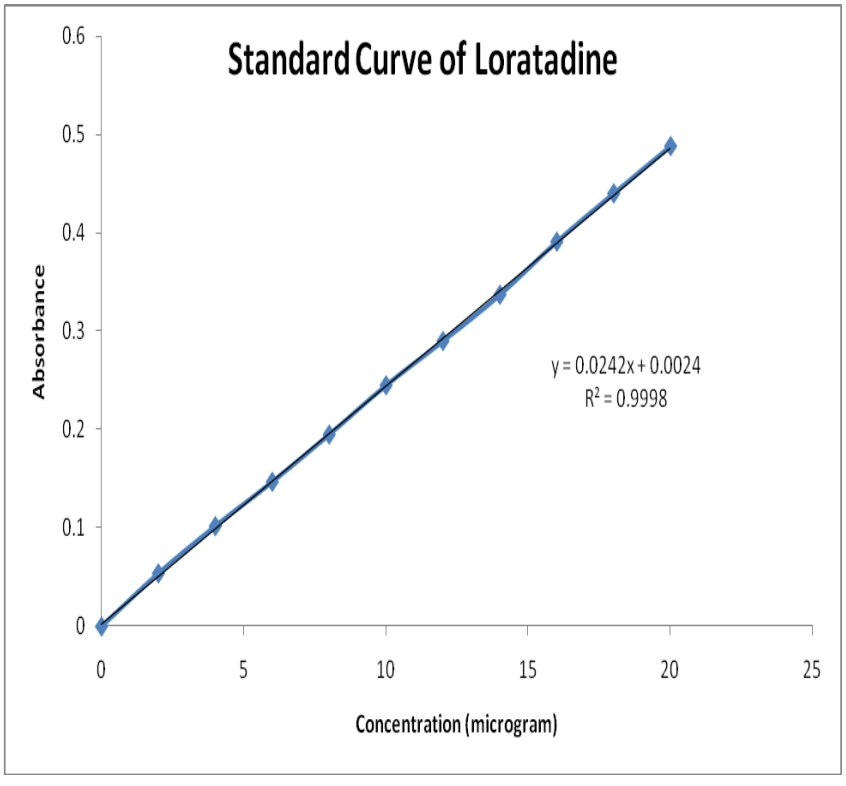


Figure 1: Standard Curve of Loratadine

In-vitro Dissolution Study of Solid Dispersion

In-vitro dissolution studies from the formulations were carried out for 1 hour in DI water. The solid dispersion was subjected to the paddle dissolution method using 900 ml DI water. The dissolution test was performed at 100 rpm and the temperature was set at $37^0C \pm 0.5^0C$. At different interval (5 min, 10 min, 15 min, 20 min, 30 min, 40min, 50 min & 60 min) samples of 10 ml were withdrawn, filtered and assayed by spectrophotometer (UVmini-1240, Shimadzu Corporation, Japan) at 280 nm. After each sampling, equal volume (10 ml) of fresh DI water with the same temperature was replaced. It was made clear that none of the ingredients used in the formulations interfered with the assay.

Flow chart for the process of preparation of Solid Dispersion:

Solvent Evaporation Method

Poorly water-soluble drug

Loratadine

+

Polymers

+

Solvent

Methanol

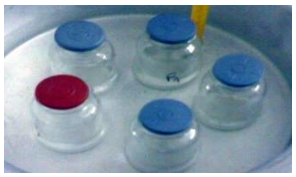
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Solvent evaporation resulting Solid Dispersion

+

Bulking Agent

Lactose



Prepared formulations

Table 4: Formulation Series-1

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Loratadine	100	100	100	100	100	100	100	100
Peg 6000	250							
Poloxomer 188		250						
Poloxomer 407			250					
HPC				250				
HPMC					250			
Cros Povidone						250		
Cros Carmellose							250	
Kollicoat IR								250
Lactose(gm)	1	1	1	1	1	1	1	1
Methanol(ml)	4	4	4	4	4	4	4	4

Table 5: Formulation Series-2

Ingredients (mg)	F-9	F-10	F-11	F-12	F-13	F-14	F-15	F-16
Loratadine	100	100	100	100	100	100	100	100
Peg 6000	500							
Poloxomer 188		500						
Poloxomer 407			500					
HPC				500				

Table 5: Formulation Series-2

Ingredients (mg)	F-9	F-10	F-11	F-12	F-13	F-14	F-15	F-16
HPMC					500			
Cros Povidone						500		
Cros Carmellose							500	
Kollicoat IR								500
Lactose(gm)	1	1	1	1	1	1	1	1
Methanol(ml)	4	4	4	4	4	4	4	4

Result and Discussion

Loratadine is one of the most commonly used anti-histamine. It is practically insoluble in water[6] but highly permeable through physiological membrane. The present study was aimed to observe release pattern of drug by solid dispersion method. Solubility was increased by using different polymers such as, Peg 6000, Poloxomer 188 & 407, HPC, HPMC, Crospovidone, Croscarmellose and Kollicoat IR. The efficacy of these pharmaceutical excipients on drug release was evaluated by in-vitro dissolution. The variables affecting drug dissolution was pharmaceutical excipients/polymers loading and physicochemical property of the drug molecule.

Effect of Polymers on the release of Loratadine from solid dispersion

Figure 2 and 4 are showing the release profile of Loratadine from the solid dispersion of Peg 6000, Poloxomer 188 & 407, HPC, HPMC, Crospovidone, Croscarmellose and Kollicoat IR. Figure 2 is showing the release from 71% polymer and figure 4 is showing the release from 83% polymer. % Release is plotted against time. In both cases, release was increased with the increase of polymer. In figure 6, % release of Loratadine within 10 minutes has been shown. Significant % release was observed in HPMC formulation. With the increase of HPMC from 71% to 83%, release was increased from 61.86% to 71.88% after 60 minutes. Table 6 & 7 are showing the R^2 value of the formulations. All the formulations followed first order release kinetics.

Table 6: R^2 value of different formulations having 71% polymer		
Formulations	Zero Order	First Order
F-1	0.712	0.892
F-2	0.650	0.853
F-3	0.832	0.984
F-4	0.522	0.904
F-5	0.525	0.914
F-6	0.710	0.956
F-7	0.581	0.990
F-8	0.583	0.968

Table 7: R^2 value of different formulations having 83% polymer		
Formulations	Zero Order	First Order
F-9	0.656	0.871
F-10	0.825	0.967
F-11	0.811	0.973
F-12	0.581	0.953
F-13	0.425	0.974
F-14	0.624	0.913
F-15	0.553	0.970
F-16	0.649	0.980

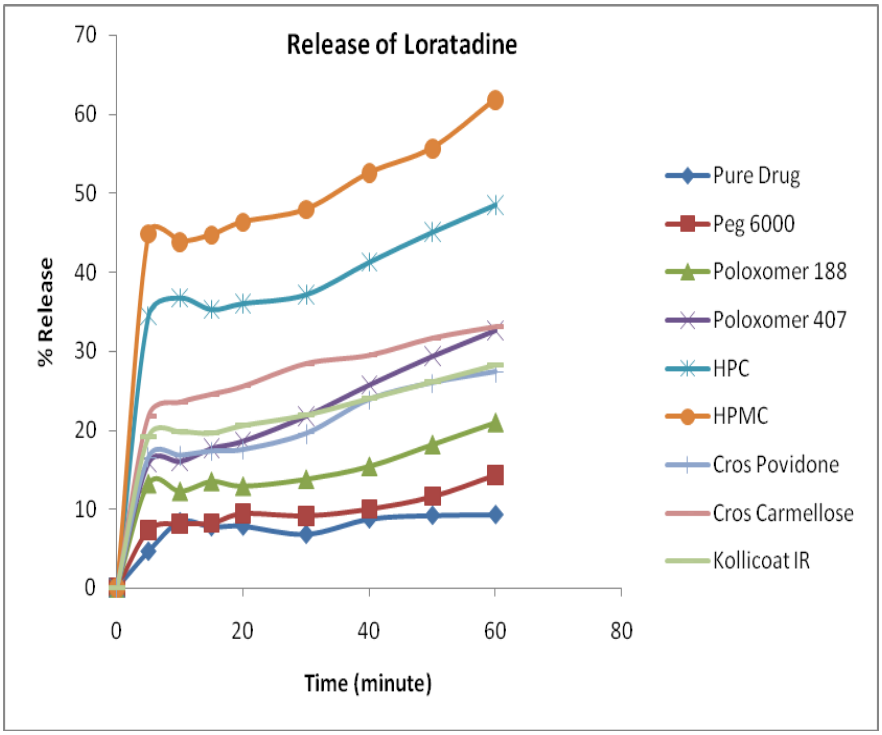


Figure 2: % Release of Loratadine from solid dispersion of different Polymer (71%)

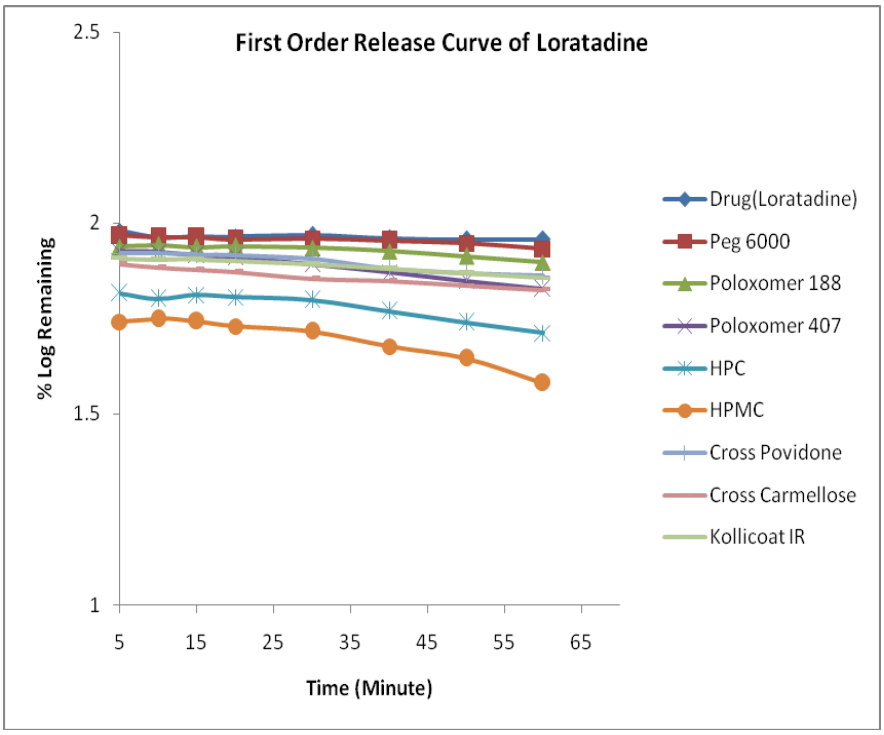


Figure 3: First order release of Loratadine from solid dispersion of different Polymer (71%)

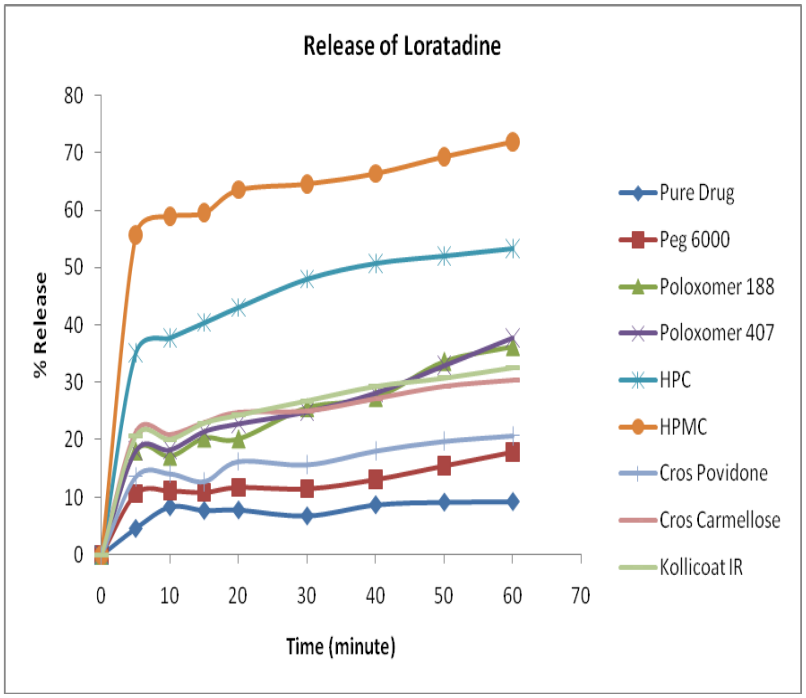


Figure 4: % Release of Loratadine from solid dispersion of different polymer (83%)

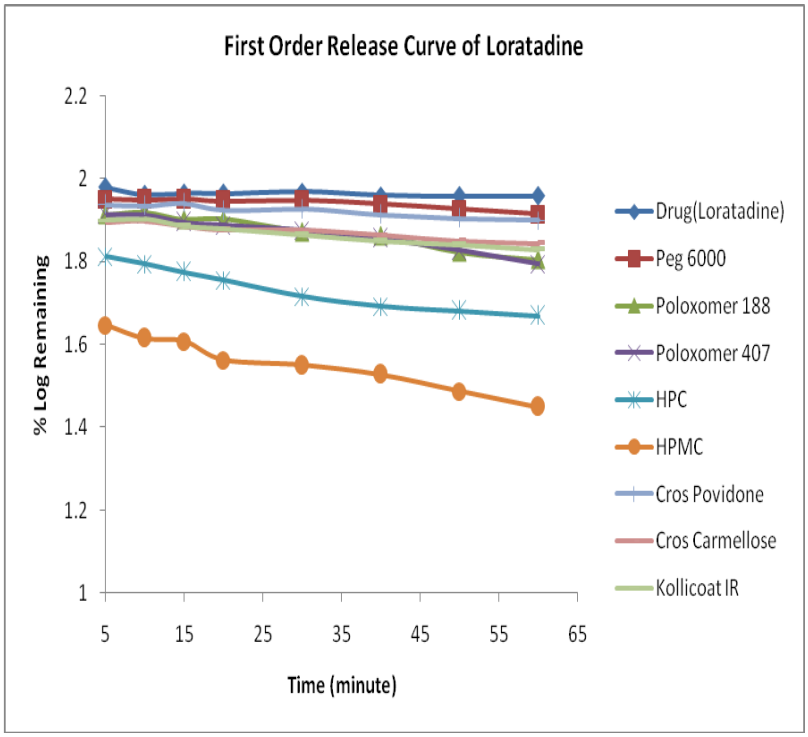


Figure 5: First order release of Loratadine from solid dispersion of different Polymer (83%)

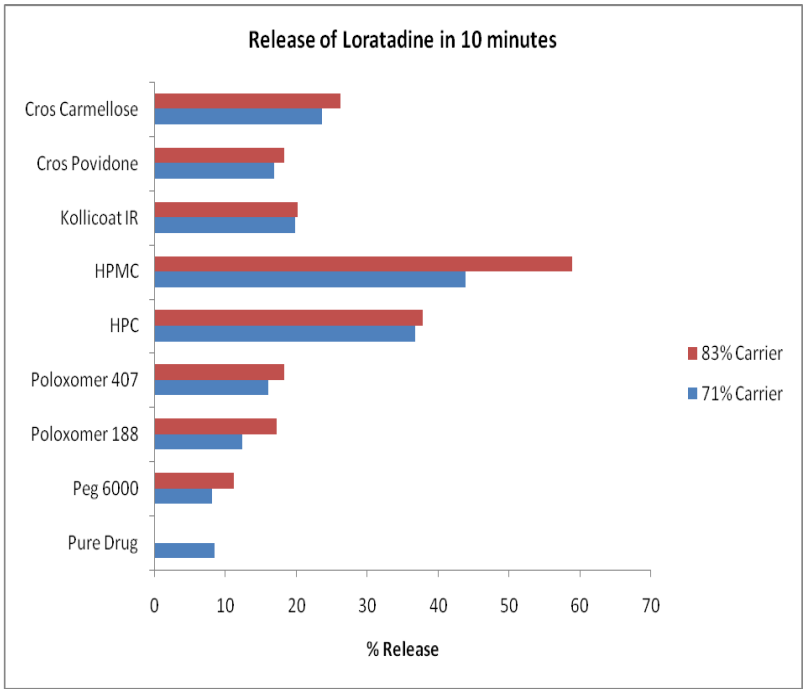


Figure 6: % Release of Loratadine from solid dispersion of different polymer within 10 minutes

Conclusion

Loratadine is a practically insoluble drug. To increase its solubility in water, different polymer-carriers were used by solid dispersion method. In first case, Peg 6000, Poloxomer 188, Poloxomer 407, HPC, HPMC 5cps, Crospovidone, Croscarmellose and Kollicoat IR were assessed for this method as carrier. HPMC 5cps based formulation shows significant improvement in dissolution or solubility of Loratadine in water. HPMC based solid dispersion formulation can be a way to improve dissolution of loratadine in commercial production.

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