RESEARCH ARTICLE

Formulation and *In vitro* Evaluation of Domperidone as Solid Dispersion Tablet

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ABSTRACT

In this study, we need to enhance the solubility of the domperidone drug of Class II in the biopharmaceutics classification system and enhance the *in vitro* dissolution by forming a solid dispersion by two methods solvent evaporation and fusion method. In solid dispersion formation study, we used poloxamer188, poloxamer407, and peg6000 in different proportion (1:1, 1:3, and 1:5) to study their effect of them on solubility and dissolution, the polymer that gives high solubility and high percent of drug release in first 20 minutes is PEG6000 in ratio (1:5) (F15) that prepared by solvent evaporation. X-ray powder diffraction (XRD), Fourier transforms infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC) are used to characterize and evaluate solid dispersion.

Keywords: Characterization, Drugs, Solubility.

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INTRODUCTION

Domperidone has a chemical formula 5-chloro 1-(1-(3-(2,3-dihydro2-oxo-1- h-benzimidazol-1-yl)-propyl)4-piperidinyl)1,3-dihydro-2h-benzimidazol-2-one, and a structure shown in figure 1. The drug acts as a dopamine receptor antagonist used to treat nausea and vomiting.[1] It has a Mw 425, Mp 242–248ºC and has molecular formula a C22H24ClN5O2.[2]

Domperidone is classified as class II in pharmaceutical classification system which consider to has practical insolubility in water, and slightly solubility in alcohol (methanol, ethanol), domperidone has first pass metabolism in liver and it is bioavailability not exceed 20%.[3]

Oral dosage form is the most widely dosage form used as it easier to use and is more convenient but the most problem associated with it is the bioavailability of the drug that belong to class II and class IV that have low solubility,so there are many technique that resolve this problem such as decreasing particle size, lipid phase system, solid dispersion system.[4]

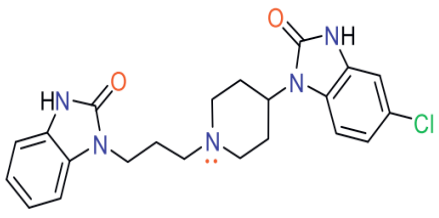

Figure 1: Domperidone structure

Solid dispersion is a modern dosage form used to increase bioavailability and dissolution of drugs with a problem in dissolution step, limiting step, by solid dispersion problems associated with other methods such as solubilization (by cosolvent), reduction of particle size, and salt formation is negligible.[5] Hence, solid dispersion is the most promising method for increasing solubility, it means dispersed of active pharmaceutical ingredient in an polymer (inert matrix), several techingues are used for preparing solid dispersion such as fusion, solvent evaporation, lyophilazation.[6] The increasing dissolution and bioavailaibility of poorly soluble drugs is by reducing particle size, converting the drug to amorphous form and increasing wettability,solid dispersion is considered an intermediate product that most incorporated into final dosage form.[7] there are three classes of solid dispersion in class 1 urea and mannitol are used to increase the solubility of drug as a crystalline polymer and is thermodynamically unstable, class 2 is thermodynamically stable that use amorphous polymer like PEG, HPMC, pvp, and cyclodextrin. This polymers increase drug solubility by decreasing particle size and increasing wettability, and class 3 SD is a new class developed in this. Class surfactants can be used in combination with hydrophilic polymer or alone, poloxamer 407, poloxamer188, Gelucire 44/14 are polymers used in this type and increase aqueous solubility by 8-10 fold when compared with pure drug.[8] Solid dispersion has three generations. First-generation leads to the formation of crystalline solid dispersion by using crystalline carriers like urea and mannitol.[9] Second generation contain

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a hydrophilic carrier in an amorphous state like polyethylene glycol, hdroxypropylmethyl cellulose, and hydrophobic drug.[10] Third generation, the carrier her is an amorphous and surfactant polymer.[11]

MATERIAL

Domperidone (gift from Pioneer pharmaceutical company Iraq), PEG6000 (Pioneer pharmaceutical company, Iraq), poloxamer407, poloxamer 188 (Eastman chemical company USA), methanol (Alpha Chemika)

Saturated Solubility measurement of domperidone and solid dispersion

Excess amount of DOM and solid dispersion formulas are putting in a plain tube with 10 mL distilled water and shaking at 25°C in water shaker for 48 hours, then for solid dispersion 1-mL is filtering and complete the volume for 10 mL, the concentration of DOM is analyzed spectrophotometrically at 284 nm.[12]

Calibration curve of domperidone in methanol, water, and 6.8 phosphate buffer, HCL

10 mg of domperidone is solubilized in 100 mL methanol to form a stock solution with a concentration of 0.1-mg/mL.

In water, 10mg domperidone is solubilized in 1% surfactant (tween 80) then complete volume to 100 mL to form a stock solution with 0.1 mg/mL concentration.

In 6.8 phosphate buffer, 10 mg domperidone is solubilized in 10% co-solvent (methanol), then complete volume to 100 mL to form a stock solution with 0.1 mg/mL concentration.

In 1.0N HCLPH 1.2 10 mg domperidone solubilized in 100 ml 0.1N HCL the a stock solution that formed is 0.1 mg/mL

1-mL of each solution is withdrawn and diluted to 10 mL to form concentrations 4, 8, 12, 16, 20, 24, 28, 32, 36 µg/mL, the absorbance is determined spectrophotometerically at 287 for methanol, and 284 for water and buffer.

METHOD

Here two methods, solvent evaporation method and fusion method, were used.

In solvent evaporation method, the polymer is dissolved in an organic solvent like methanol, ethanol, in a magnetic stirrer at 600 rpm until a clear solution is obtained. The active pharmaceutical drug is added while stirring is maintained for 40 min, the ratio of drug to polymer is (1:1, 1:3, 1:5) of peg6000, poloxamer 407, poloxamer 188(13). The solution is let all night for evaporation of the solvent, and then the dispersion is pulverized by mortar and pestle and sieving through sieve no.60.[14]

In the fusion method, the polymer melt in the beaker in a water bath at temperature near the polymer's melting point (PEG6000 molted at 70°C,[15] poloxamer 407 molted at 60°C,[16] poloxamer 188 molted at 65°C.[17] Then drug is added to the molten carrier and mixing until miscibility. After that the paste is removed from the water bath with continuous stirring until solidification at room temperature, then the dispersion is pulverized by mortar and pestle and sieving through sieve no.60.[18]

Drug Content

Solid dispersion equivalent to 10 mg domperidone dissolve in 50 mL methanol the solution sonicated for 10 min, 1-mL of that solution diluted to 10 mL methanol analyzed at 287 nm using UV spectrophotometer.[19]

Determination of Percentage practical yield

It is a measure to determine the efficacy of solid dispersion method and is determined by this equation.[20]

$$\text{Percentage practical yield} = \frac{\text{Weight of the prepared solid dispersion}}{\text{Actual weight of drug and carrier}}$$

No of formula	*Carrier*	*Method*	*Ratio of carrier*
F1	Poloxamer 188	Solvent evaporation	1:1
F2	Poloxamer 188	Solvent evaporation	1:3
F3	Poloxamer 188	Solvent evaporation	1:5
F4	Poloxamer 188	fusion	1:1
F5	Poloxamer 188	fusion	1:3
F6	Poloxamer 188	fusion	1:5
F7	Poloxamer 407	Solvent evaporation	1:1
F8	Poloxamer 407	Solvent evaporation	1:3
F9	Poloxamer 407	Solvent evaporation	1:5
F10	Poloxamer 407	fusion	1:1
F11	Poloxamer 407	fusion	1:3
F12	Poloxamer 407	fusion	1:5
F13	Peg6000	Solvent evaporation	1:1
F14	Peg6000	Solvent evaporation	1:3
F15	Peg6000	Solvent evaporation	1:5
F16	Peg6000	fusion	1:1
F17	Peg6000	fusion	1:3
F18	Peg6000	fusion	1:5

Apparent Solubility Test

Axcess amount of pure domperidone and solid dispersion formulation (F1-F18) were placed in 10 mL test tube containing 10 mL DW in a water shaker at 37 ± 1ºC for 48 hours, samples were withdrawn and diluted, the diluted samples were analyzed at 284 nm using UV spectrophotometer. Each sample was analyzed in triplicate and calculated mean values were considered for solubility.[21]

***In-vitro* Dissolution Studies**

In vitro drug dissolution was performed in 900 mL of pH 6.8 sodium phosphate at 37 ± 0.5 by using USP dissolution apparatus type 2, rotated 50 rpm for 60 min, at time interval 5, 10, 20, 30, 45, 60 min 5 mL sample from dissolution media withdrawn and replaces with fresh media for sink condition, these samples filtrated via a 0.45 µm filter membrane and assayed using UV-spectrophotometer at λ_{max} 284 nm.[22]

Evaluation of Selected Solid Dispersion Formula

Fourier Transforms Infrared Spectroscopy (FTIR)

To discover any interaction between drug and polymer, FTIR discovers it, the scanning rangee of domperidone and SDs formulas is 400–4700 cm^{-1} after mixing with potassium bromide (an inert matrix).[23]

Differential Scanning Calorimetry (DSC)

DSC for pure drug, peg6000 and SD(DOMP+peg6000) using DSC60 (Shimadzu, Japan), is used to study the thermal behavior of samples under rate 10ºC/min, temperature range 20–200ºC and nitrogen at a rate 20 mL/min.[24]

Powder X-ray Diffraction

X-ray for drug, polymer, and physical mixture is done and formula at 1-5 ratio is done by instrument (Model: XRD6000/ Shimadzu/Japan).[25]

Bulk and tapped density are measured by weighting 2 gm solid dispersion and pouring it in 10 mL cylinder and observing the volume of the powder and recording it, and the following equation determines bulk density

$$\text{Bulk density} = \frac{\text{(weight of the powder)}}{\text{(volume of the powder)}}$$

Tapped density is measured by tabbing the cylinder several times until the final volume is reached. After that, the volume is recorded and determined by the following equation.[26]

$$\text{Tapped density} = \frac{\text{(Weight of the powder)}}{\text{(Tapped volume of the powder)}}$$

Carr index is a measure of compressibility index and follow ability of powder.[27]

$$\text{Carr index} = \frac{\text{(Tapped density-bulk density)}}{\text{(Tapped density)}} \times 100$$

$$\text{Hausner index} = \frac{\text{(Tapped density)}}{\text{(Bulk density)}}$$

RESULT AND DISCUSSION

From saturated solubility domperidone is considered a pH-dependent drug and as it has a pka= 7.9. It considers a weak base, and its solubility in the intestine (pH 6.8) is low, so solid dispersion is one of the method that use to increase solubility in a media that has pH above 5.5.[28]

The result recorded the highest saturated solubility in ratio 1:5 of all polymers used (poloxamer 407, poloxamer188, peg6000)(0.187, 0.220, 0.191) as these polymers are hydrophilic.

Saturated Solubility of Domperidone in Different Media

Media	*Solubility (mg/mL)*
0.1N Hcl	14.61 ± 0.08
Phosphate buffer 6.8	0.0336 ± 0.05
Distilled water	0.0164 ± 0.08

Name of formula	*Carrier*	*Carrier: Drug ratio (w:w)*	*Saturated solubility (mg/mL)*
F1	Poloxamer 188	1:1	0.202
F2	Poloxamer 188	1:3	0.211
F3	Poloxamer 188	1:5	0.220
F4	Poloxamer 407	1:1	0.174
F5	Poloxamer 407	1:3	0.178
F6	Poloxamer 407	1:5	0.187
F7	PEG6000	1:1	0.128
F8	PEG6000	1:3	0.182
F9	PEG6000	1:5	0.191
F10	Poloxamer 188	1:1	0.164
F11	Poloxamer 188	1:3	0.204
F12	Poloxamer 188	1:5	0.210
F13	Poloxamer 407	1:1	0.158
F14	Poloxamer 407	1:3	0.172
F15	Poloxamer 407	1:5	0.160
F16	PEG6000	1:1	0.148
F17	PEG6000	1:3	0.168
F18	PEG6000	1:5	0.172

Calibration Curve of DOM in Different Media

Dissolution

The format that gives a high water solubility (F3,F9,F15) that have a polymer ration 1:5 (poloxamer 188, poloxamer407, peg6000), respectively, the formula after 1-hour gives these result.

These formulas (F3,F6,F9)are selected to study the dissolution of them and choose the polymer that provides the high percentage of drug release in first 15 min and complete the study to form sublingual dosage form.

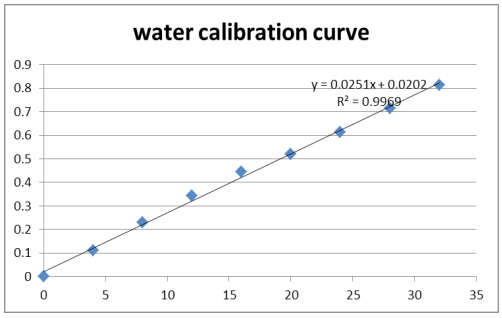

Figure 2: Calibration curve in water

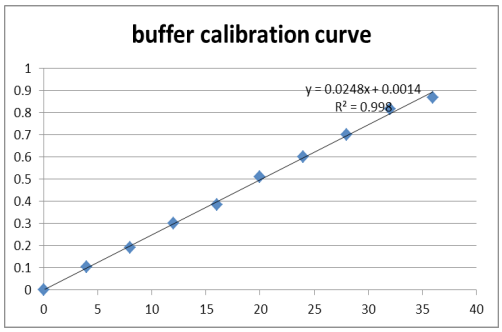

Figure 3: Calibartion curve in 6.8 Ph buffer

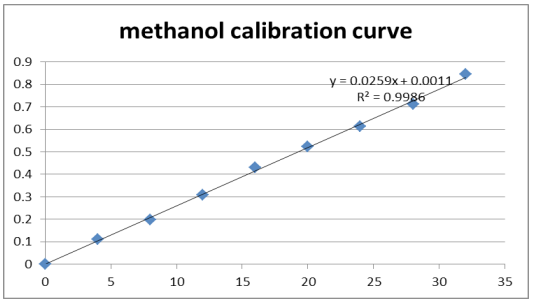

Figure 4: Calibration curve of domperidone in methanol

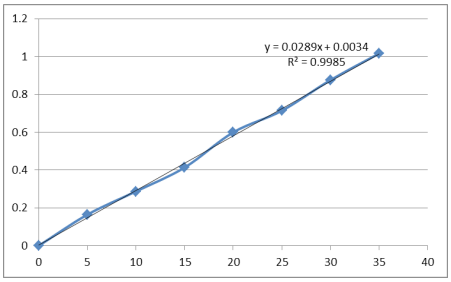

Figure 5: Calibration curve in 0.1NHCL

All these polymers increase the dissolution rate in comparison with pure drug

In comparison between polymers and between F9 and F6, we found the dissolution of peg6000 is more than poloxamer 407 (f2=25), but when comparing F9 with F3, the same enhancement of dissolution in obtained (f2=37).

As peg6000 increases the dissolution of domperidone in first 15 minutes to approximately 66%.

Infra-red Spectral Studies

The FTIR of pure drug and 1:5 solid dispersion (DOMP + PEG6000) show in Figures 7 and 8, respectively.

- A pure drug shows a characteristic peak at 3070 cm^{-1} (H bonded of NH), 1685cm^{-1} (C=O), 1103 cm^{-1} (C-N).
- Symmetric and asymmetric C-H stretching appear at 2819.93 cm^{-1}, 2935.66 cm^{-1}, respectively.
- 1624.06 cm^{-1} is a band of an aromatic C = C stretching.
- The infrared spectrum of 1:5 domperidone and peg6000 solid dispersion indicate no interaction between polymer and drug during the preparation of solid dispersion.

Differential Scanning Calorimetry (DSC)

Thermal behavior of domperidone pure drug and solid dispersion are show in figure

Domperidone show a sharp peak at 252°C

Disappearing the domperidone peak and replaced by polymer's melting point indicate convert of fully crystalline domperidone to amorphous form.

Powder x- ray diffraction is done to study the conversion of drug from crystal in pure drug to amorphous in the solid dispersion .

Pure drug and formula are shown in Figures 11 and 12, respectively.

% of drug release in 900 mL dissolution media			
Time	*F3 (Poloxamer 188)*	*F6 (Poloxamer 407)*	*F9 (PEG6000)*
5	50.9	32	55
10	55	44	61
20	60	54	66
30	77	68	71
45	86	75	78
60	96	80	84.2

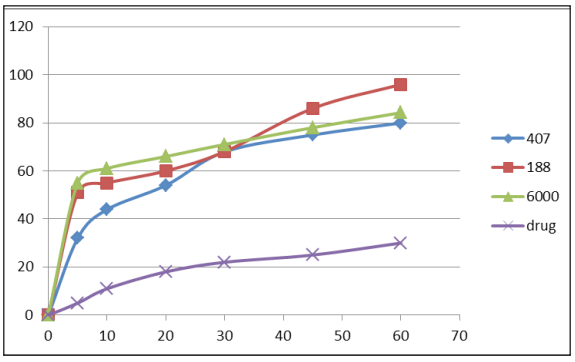

Figure 6: Dissolution of formulas with high water solubility

Drug Content

Formula name	*Preparation method*	*(PY %)*	*Drug content mean ± SD (n=3)*
F1	Solvent evaporation	97.3	95.4 ± 0.01
F2	Solvent evaporation	96.3	93.9 ± 0.02
F3	Solvent evaporation	97.57	96.15 ± 0.04
F4	Solvent evaporation	94.38	85.65 ± 0.02
F5	Solvent evaporation	98.1	94.15 ± 0.06
F6	Solvent evaporation	98.07	93.13 ± 0.02
F7	Solvent evaporation	97.03	99.48 ± 0.01
F8	Solvent evaporation	96.75	92.8 ± 0.01
F9	Solvent evaporation	97.78	98.16 ± 0.08
F10	Hot melt-fusion	94	95.05 ± 0.02
F11	Hot melt-fusion	97.5	96.1 ± 0.02
F12	Hot melt-fusion	97.5	96.9 ± 0.04
F13	Hot melt-fusion	98.8	97 ± 0.08
F14	Hot melt-fusion	97.5	94.6 ± 0.03
F15	Hot melt-fusion	94.6	95.05 ± 0.01
F16	Hot melt-fusion	96.6	97 ± 0.02
F17	Hot melt-fusion	98.5	96 ± 0.03
F18	Hot melt-fusion	96.9	94 ± 0.02

Evaluation parameter	*Value*
Angle of repose	320
Bulk density (gm/mL)	0.5
Tapped density (gm/mL)	0.57
Carr's index %	12.28
Haunser's ratio	1.14
Type	Good

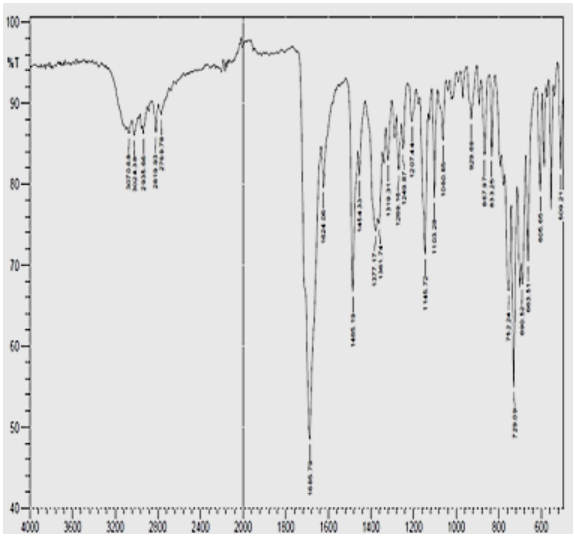

Figure 7: FTIR of domperidone

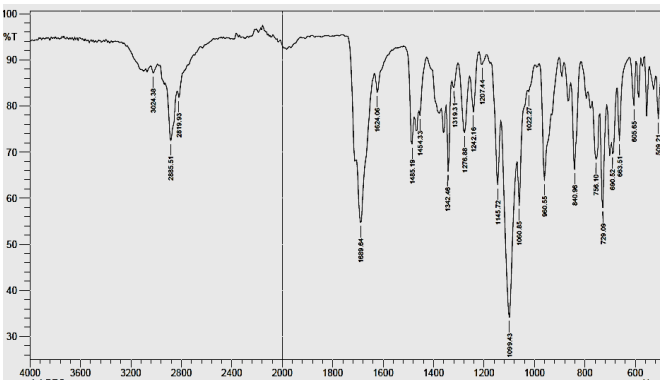

Figure 8: FTIR of DOM+peg6000

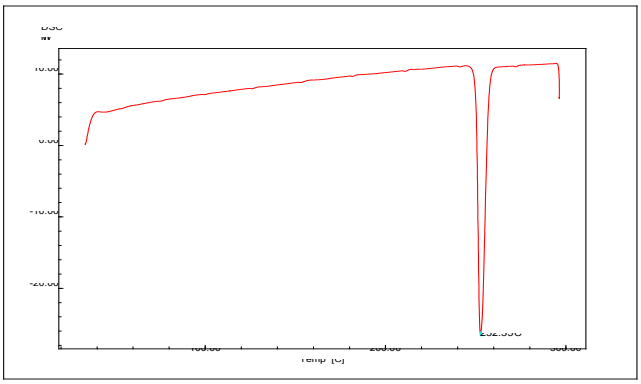

Figure 9: DSC of domperidone

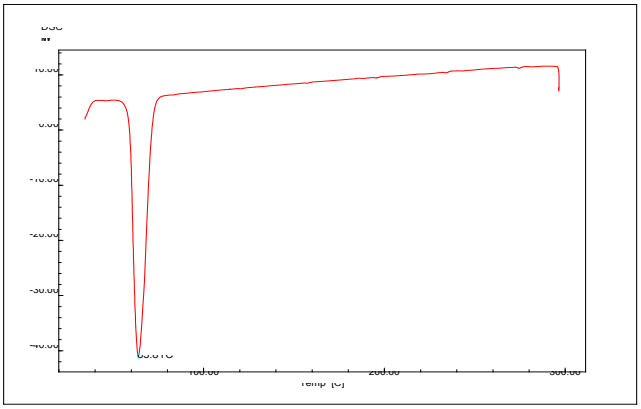

Figure 10: DSC of selected formula drug+ peg6000

Pure drug has strongest peak was observed in 14.06°, 22.5°, 15.6°.

With intensity at 1902, 1394, 928 which respectively, the x-ray diffraction of DOMP-peg6000 solid dispersion show disappear of domperidone sharp peaks, and appear of few distinctive peakes this is an indication of lower the crystallinity of domperidone.[29,30]

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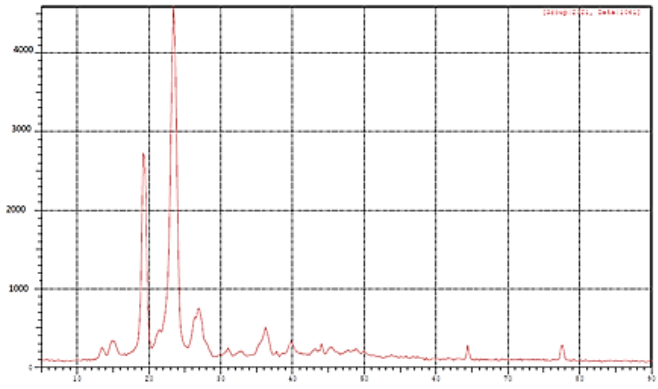

Figure: 12 x-ray of peg6000+domperidone

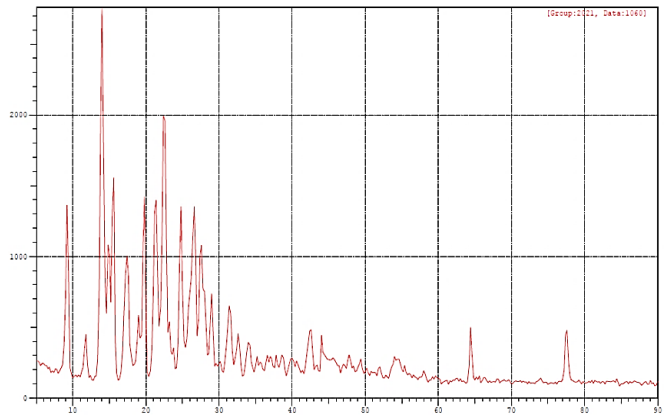

Figure 11: x-ray of domperidone

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