Research Article

Development and Evaluation of Gastroretentive Floating Tablets of Cefpodoxime Proxetil

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ABSTRACT

The floating drug delivery systems (FDDS) that can be retained in the stomach for a prolonged period of time and gives therapeutic action in a predetermined manner. In this study, we design and evaluated floating matrix tablets of Cefpodoxime Proxetil, to prolong gastric residence time and increase drug absorption further increasing the bioavailabilityIn this study, we design and evaluated floating matrix tablets of Cefpodoxime Proxetil, to prolong gastric residence time and increase drug absorption further increasing the bioavailabilityIn this study, we design and evaluated floating matrix tablets of Cefpodoxime Proxetil, to prolong gastric residence time and increase drug absorption further increasing the bioavailability.A simple visible Spectrophotometric method has been employed for the estimation of Cefpodoxime Proxetil at 263 nm and Beer's law is obeyed in the concentration range of 5-40 μg/ml. Preformulation studies were carried out to optimize the required quantity for HPMC (K4M). Sodium CMC, carbopol 934P was used in different concentrations.Total 7 formulations were prepared. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. The tablets were prepared by direct compression technique, using polymer such as hydroxy propyl methyl cellulose (HPMC K4M),sodium CMC and carbopol 934P in different combinations with other standard excipients like sodium bicarbonate, lactose and Magnesium stearate used as gas generating agent, as filler and as lubricant respectively. Tablets were evaluated for physical characterization viz.hardness, friability, swelling index, floating capacity, thickness and weight variation. Further tablets were evaluated *in-vitro* drug release for 12 hr.

Keywords: Cefpodoxime Proxetil, swelling index, floating capacity, HPMC, Sodium CMC.

INTRODUCTION

Oral route is the most convinient and extensively used route for drug administration.Over the years the oral dosage forms have become sophisticated with development of controlled release drug delivery system (CRDDS).This route has high patient acceptability, due to ease of admistration. Controlled release drug delivery system release drug at predetermined rate, as determined by drug's pharmacokinetics and desired therapeutic concentration. This helps in achieving predictable drug plasma concentration required for therapeutic effect. A number of oral controlled release systems have been developed to improve delivery of drugs to the systemic circulation Cefpodoxime proxetil is a third generation cephalosporin prodrug, having a white to light brownish white powder, odourless, slightly soluble in water, ether; freely soluble in dehydrated alcohol; soluble in acetonitrile & in methyl alcohol which is administered orally. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50%.Floating drug delivery is able to prolong the gastric retention of drug and thereby possibly improve oral bioavailability of cefpodoxime proxetil The half life of cefpodoxime proxetil is 2.2 hours. In the present study it is intended to formulate and evaluate the floating multiparculate drug delivery system for increasing the bioavailability of cefpodoxime proxetil. Formulation of Floating beads containing cefpodoxime proxetil as a drug candidate which would remain in stomach and/or upper part of GIT for prolonged period of time thereby maximizing the drug release at desired site within the time before Gastroretentive floating drug delivery system (GRFDDS) left the stomach and /or upper part of GIT. Cefpodoxime proxetil is a beta lactum antibiotic. Its action is by binding to specific penicillinbinding proteins (PBPs) located inside the bacterial cell wall; it inhibits the bacterial cell wall synthesis. It is highly stable in the presence of beta- lactamase enzymes.

MATERIALS AND METHODS

Materials

Cefpodoxime proxetil was procured as gift sample from Aurbindo pharmaceutical, chandigarh.HPMC obtained by Centre drug

laboratory delhi., Sodium bicarbonate purched from centre drug house delhi.

METHOD

Formulation of Floating Tablet

Each floating tablets containing 100 mg Cefpodoxime Proxetil were prepared by direct compression method. Cefpodoxime pure drug was mixed with required quantity of HPMC K4M,sodium CMC, carbopol 934P, sodium bicarbonate and lactose by geometric mixing inmortar and pestle for 10 min. The above powder was lubricated with magnesium stearate in mortar and pestle for 2min.The lubricated blend was compressed into tablets using 12 mm flatface round tooling on CLIT Pilot Press rotary tablet machine5,6,7. Compression force was adjusted to obtain tablets of hardness 6-9 kg/cm2 with 4.0 mm tablet thickness (Table no.1).

Table 1: Composition of floating tablets of cefpodoxime proxetil Ingredient (mg) B1 B2 B3 B4 B5 B6 B7

Cefpodoxime Proxetil	200	200	200	200	200	200	200
HPMC K4M	100	100	100	100	100	100	100
Guar Gum	45	40	35	30	25	20	15
Carbopol 934P	20	20	20	20	20	20	20
Lactose	94	99	104	109	114	119	124
Sodium bicarbonate	85	85	85	85	85	85	85
Magnesium stearate	6	6	6	6	6	6	6
Total weight of tablets	550	550	550	550	550	550	550

Evaluation of Granules

Angle of repose

The angle of repose of powder blend was determine by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter ofthe powder cone was measured and angle of repose was calculated**.**The angle of repose of CefpodoximeProxetil was determined by fixed funnel method. The loose bulk density (LBD) and tapped bulk densities (TBD) were determined by using measuring cylinder**.**

Compressibility Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down**.**The Carr's index (%) and the Hausner ratio were calculated using following equations .

$$Carr,s\ index = \frac{TBD-LBD}{TBD} \times 100$$

$$\text{Hausner Ratio} = \frac{TBD}{LBD} \times 10$$

Evaluation of Tablets

Physical properties like Weight variation, Hardness, Thickness, Friability and Drug content of tablet performed and results shown in Table No.2.

Thickness

Thickness of tablets was determined using Vernier caliper. Five tablets were randomly selected for the determination of thickness and diameter with the help of vernier caliper.

Average weight

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu).

Drug content

Twenty tablets were crushed and powder equivalent to weight of tablet dissolved in 0.1 N HCl. Then suitable dilutions were made and absorbance at 263 nm wavelength was taken by using a UV spectrophotometer. Drug content was estimated spectrophotometrically at 263 nm .

Hardness

The resistance of tablets to shipping or breakage, under conditions of storage,transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester10. The hardness was measured in terms of kg/cm^2.

Friability

This was determined by weighing 10 tablets after dusting, placing them in the friabilator and rotating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the total

remaining weight of the tablets was recorded and the percent friability was calculated

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Determination of swelling index

The swelling properties of floating tablet containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of distilled water at 37 .05^{0}C paddle rotated at 50 rpm. The tablets were removed periodically from dissolution medium. After draining free from water by blotting paper, these were measured for weight gain.Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation shows relationship between swelling index and time.

$$\text{WU \%} = \frac{\text{Weight of swollen tablet} - \text{Initial weight of the tablet}}{\text{initial weight of the tablet}} \times 100$$

Buoyancy determination

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remained buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of floatation i.e. as long the dosage form remains buoyant is called Total Floating Time (TFT).The buoyancy test of tablet was studied by placing them in 500 ml beaker containing 0.1 N HCl, then tablet from same batches were placed in dissolution test apparatus containing 900 ml 0.1N HCl, maintained at 37±0.5^{0}C and agitated at 50 rpm. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation.

***In Vitro* Release Studies**

The *in vitro* dissolution test was performed using USP type II dissolution test apparatus. *In* vitro dissolution studies of prepared drug were carried out in 900 ml of 0.1 N HCl as a medium using USP type 2 test apparatus with three replicates. The paddle rotation speed was 75 rpm, and a temperature of 37.01°C was maintained. In all experiments, 5 ml of dissolution sample was withdrawn at 5min interval, filtered using a 0.45-mm whatman filter, and replaced with an equal volume of fresh medium to maintain a constant total volume. Samples wereanalysedon UV/Visible spectrophotometer at 263nm**.**

RESULTS AND DISCUSSION

The observed melting point ranged between 155-1600^{0}c. The reported melting point values for cefpodoxime proxetil was in the range of 1600^{0}c. The absorption maxima of the standard solution were scanned between 200-400 nm region on shimazdu 1800 spectrophotometer. Theabsorption maxima were found to be 263 nm.Infrared spectrum shows all prominent peaks of cefpodoxime proxetil. IR spectrum indicated that characteristics peaks belonging to measure functional group such as principle peak at wave number 2937.04,2984.39,3330.81,1618.05 and 1638.19cm-1.The major IR peaks observed cefpodoxime proxetil were 2937.04(C-H), 3330.81(N-H), 1638.19(C=N),1074(C-O), 1761(C=O), 1274(C-N), 1375(C-H) . The infrared spectrum of physical mixture of polymers (HPMC K4M) and cefpodoxime proxetil was studied and confirmed that there is no interaction with each other. The spectra show all the prominent peaks of drug as well as polymer. IR spectrum indicated characteristics peaks belonging to measure functional group
such as principle peaks at wave no. 2941.53, 2984.33, 3332.64, 1623.67 and 1628.19.Hence it can be concluded that there were no any significant changes in the physical mixture of cefpodoxime proxetil and HPMC K4M. All formulation from B1 to B7 was evaluated with thickness and diameter of tablets measured by vernier caliper. Thickness and diameter was in range of 3.90±0.04 to 4.25±0.04.The hardness was in range of 12.01±0.07 to 12.21±0.04kg/cm2,which was measured on Monsanto hardness tester. Drug content release was in the range of 98.68±0.20 to 107.73±0.13 shown in (Table 2). The percentage drug release was found 50% after 7 hrs.for all the formulations B1-B7. After12 hrs.it showed 79% drug release shown in Table no.3.The swelling index was calculated with respect to time. As time increase, the swelling index was increased because weight gain by tablet was increased proportionally with rate of hydration,later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution

medium. The direct relationship was observed as shown in (Table no.4).The release rate can be controlled depending upon the type and concentration of the polymer that swells,leads to diffusion and erosion of the drug. In view of this absorption characteristics, the hypothesis of current investigation is that if the gastric residence time of cepfodoxime proxetil containing formulation is prolonged and allow to float in the stomach for a long period, the oral bioavailability might be increased hence the present research work was to study systematically the effect of formulation variable on the release and floating properties of cepfodoxime proxetil drug delivery system. For floating drug delivery system,the polymers used must be highly swellable in shortest time. Hence, HPMC was chosen as a main swellable polymeric material. In order to get the longer duration of floating time the high viscosity polymer selected, HPMC K4M was chosen and it was found that, increased viscosity of a polymer prolongs the drug delivery from thedosage form. In order to retain the dosage form in the stomach for a long period of time and to avoid gastric emptying dosage form,carbopol 934P was included. It was reported earlier that, Carbopol belongs to the class of swellable and adhesive polymers and to utilize this property of carbopol,it was included in the formulation with the intention of adhering the dosage form to the inner wall of the stomach and also possibly to control the release of cepfodoxime proxetil from the dosage form. Total floating time depends upon the amount of HPMC as the polymer content increased the floating time was increased due to the formation of thick gel which entrapped the gas formed due to NaHCO3 firmly. Due to high viscosity and content of the polymer bursting effect of the tablet was decreased and float for longer duration of time. From the result of floating lag time it was concluded that, as the concentration of gas generating agent increase the floating lag time get shortens this finding were supported by study of Park et al., reported that as the concentration of gas generating agent (NaHCO3) was increased the floating lag time get shortened and at the same time floating ability get increased. Carbopol was used as a swelling agent, which also helped in gastric retention due to its adhesive properties. But carbopol affected floating properties.Physicochemical evaluation i.e. the prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. The evaluated parameters were within acceptable range for all the formulations. Results of Water uptake study showed that the order of swelling in these polymers could indicate the rates at which the preparations are able to absorb water and swell. Maximum liquiduptake and swelling of polymer was achieved upto 10 hrs and then gradually decreased due to erosion.

CONCLUSION

The weighed quantities of drug and polymers were mixed thoroughly in different ratios and HBS tablets were prepared by direct compression method. The prepared HBS tablets were evaluated The prepared tablets of all the formulations were evaluated for precompression parameters like angle of repose, bulk and tapped density and compressibility index and physical characters like tablet hardness, friability, weight variation, buoyancy lag time, total floating time, Swelling index, *in-vitro* drug release.

Table 2: Physiochemical Properties of Cefpodoxime Floating Tablets

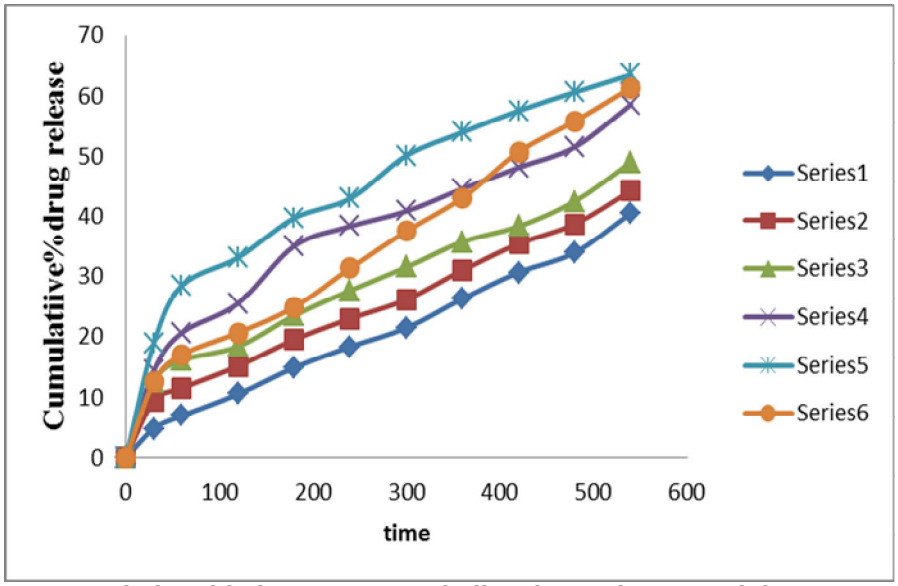
Batch code	Average weight	Thickness (mm)	Hardness (kg/cm2)	Diameter (mm)	Friability (%)	Drug content (%)
B1	550	4.25 ± 0.04	12.05± 0.07	7.7± 0.06	0.70±0.065	104.48 ± 0.20
B2	540	4.00 ± 0.05	12.02 ± 0.03	7.0± 0.02	0.91±0.044	101.58 ± 0.20
B3	555	3.90 ± 0.03	12.04 ± 0.06	8.3± 0.05	0.71±0.080	99.38 ± 0.21
B4	565	4.20 ± 0.06	12.21 ± 0.04	8.1± 0.06	0.72±0.042	98.68 ± 0.20
B5	550	4.10 ± 0.05	12.01 ± 0.07	7.6± 0.07	0.80±0.066	106.28 ± 0.10
B6	545	3.90 ± 0.04	12.07 ± 0.05	7.6± 0.07	0.76±0.054	107.73 ± 0.13
B7	560	3.85 ± 0.07	12.10 ± 0.03	9.2± 0.03	0.75±0.045	103.36 ± 0.14

Table 3: Dissolution drug release data of batch B1 to B6

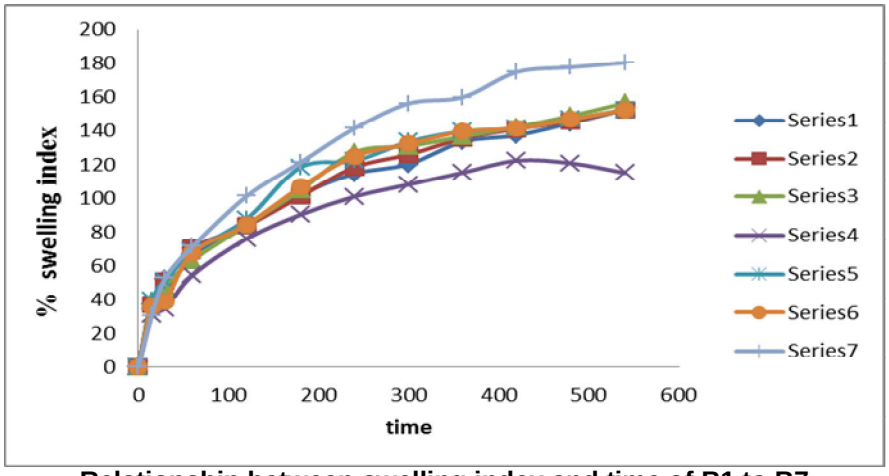
Time(min)	Cumulative %drug release					
	B1	B2	B3	B4	B5	B6
0	0.000	0.000	0.000	0.000	0.000	0.000
30	4.786	9.349	12.543	14.368	18.931	12.543
60	6.917	11.505	16.086	20.659	28.442	16.999
120	10.520	15.134	18.371	25.521	33.076	20.657
180	14.873	19.512	23.497	34.978	39.652	24.883
240	18.337	23.001	27.647	38.278	42.978	31.322
300	21.454	26.144	31.500	40.821	50.109	37.477
360	26.277	30.992	35.692	44.608	53.947	43.072
420	30.624	35.364	38.265	48.141	57.531	50.704
480	33.899	38.665	42.493	51.510	60.585	55.776
540	40.473	44.264	49.025	58.547	63.472	61.332

Table 4: swelling index of batch B1 to B7

Time (min)	% swelling index						
	B1	B2	B3	B4	B5	B6	B7
0	0	0	0	0	0	0	0
15	37	37	38.6	31.14	39.38	36	30.5
30	52.38	50.9	48	34.71	50.92	39	52.7
60	66.73	70.15	63.15	54.35	68.23	67.5	71.2
120	83.61	83.6	83.9	75.8	87.46	84.18	100.85
180	102	100.9	104.66	90.07	118.2	106.4	121.22
240	114.38	118.23	127.3	100.78	122.07	124.9	141.6
300	120.15	125.9	131	107.92	133.61	132.33	156.4
360	133.61	135.53	136.7	115	139.74	139.74	160.11
420	137.46	141.3	142.39	122.21	141.6	141.6	174.9
480	144.84	145.84	149.05	120.65	147	147	177.77
540	152.84	152.84	156.69	114.84	152.7	152.7	180.48

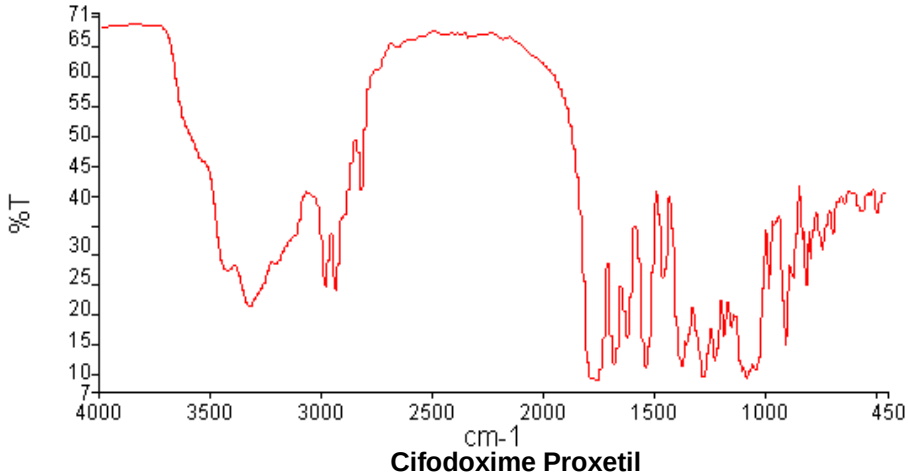


Relationship between cumulatiive drug release and time



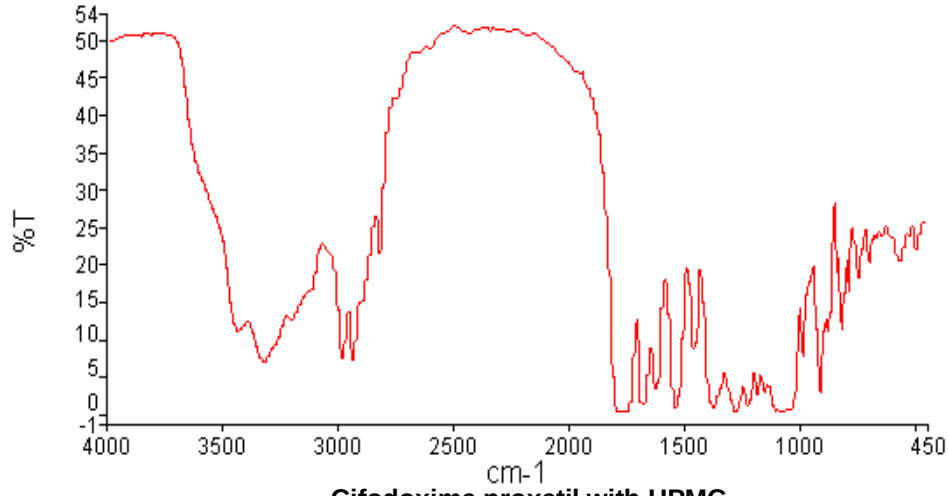
Relationship between swelling index and time of B1 to B7

Compatibility study of drug and excipient



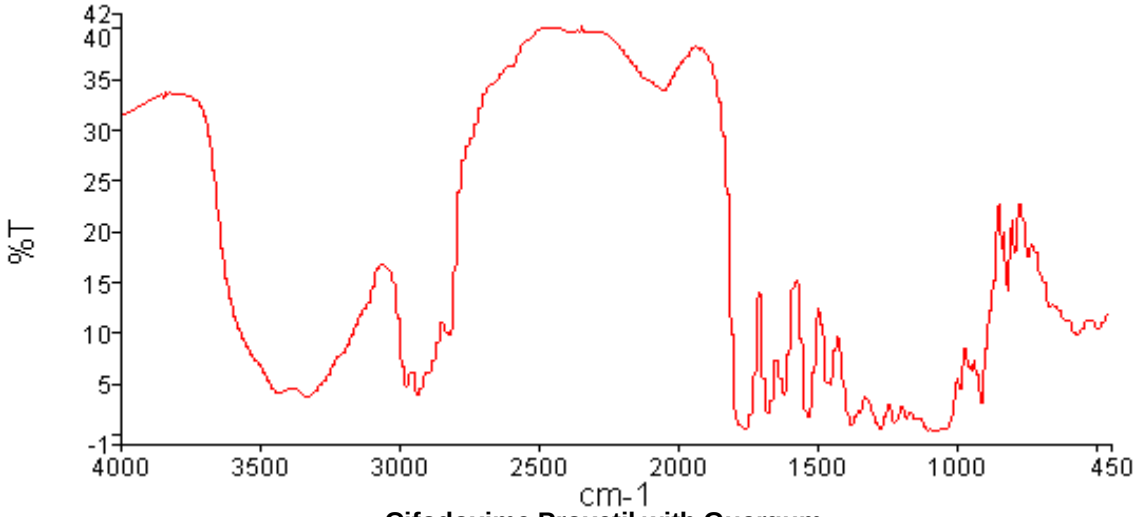
Cifodoxime Proxetil

Fig. 2: FTIR of Cifodoxime proxetil



Cifodoxime proxetil with HPMC

Fig. 3: FTIR of Cifodoxime proxetil with HPMC



Cifodoxime Proxetil with Guargum

Fig. 4: FTIR of Cifodoxime Proxetil with Guargum

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