Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 3, 2012

Research Article

FORMULATION AND PHARMACOKINETIC STUDY OF FAMOTIDINE LOADED FLOATING MICROBALLOONS

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Received: 1 Feb 2012, Revised and Accepted: 16 March 2012

ABSTRACT

Floating microballoons of famotidine were prepared by the Solvent diffusion and Evaporation method, using acrylic polymers dissolved in the mixture of Dichloromethane, Ethanol and Isopropyl alcohol. The effect of the various formulation parameters on the morphology, drug Incorporation efficiency, In-vitro floating behavior, particle size distribution, along with In-vivo bioavailability of Famotidine were studied. The prepared Microballoons were spherical in shape with porous smooth surface, the Microballoons showed the good in vitro floating behavior. The release rate of the drug was significantly affected by the type of combination and amount of the polymer used. It was observed that the size of Microballoons was strongly depend on the amount of polymer and the solvent system. The In-vitro study suggested that the Microballoons could float for a longer period of time and the in-vivo study supported the in vitro floating characteristics of hollow Microballoons. In-vivo bioavailability studies performed on rabbits and C_{max}, t_{max} and AUC were calculated and confirmed significant improvement in bioavailability of Famotidine. The result of the present study indicate that the floating Microballoons can be successfully designed to give the controlled drug delivery and improved the oral bioavailability of Famotidine.

Keywords: Floating Microballoons, Famotidine, Solvent diffusion and Evaporation method, Acrylic polymers

INTRODUCTION

The oral route of drug administration is the most popular and convenient route but the main limitation of this route is the gastric emptying, the gastric emptying of dosage forms in humans is affected by several factors because of wide inter and intra-subject variations [1], and the rapid gastrointestinal transit can result in incomplete drug release from the device and diminished the efficacy of administered dose[2]. The incomplete release of the drug and the shorter residence time of the dosage form in the upper gastrointestinal tract, a prominent site for absorption of many drugs, will lead to lower bioavailability and drug bioavailability is a crucial fact in therapeutic effectiveness which depends on the residence time of the drug at the absorption site[3]. To overcome these problems there is the need of the gastric retention[4] and there are different approaches have been proposed to retain the dosage form in the stomach, these include bioadhesive system , swelling and expending system, effervescent system, floating drug delivery system but with the swelling and expending system there is a risk of permanent retention[5], bioadhesive system[6-8], may cause the irritation of mucus layer owing to high localized concentration of drug and the effervescent systems are unsuitable for drug degrading in basic pH because of the alkaline microenvironment. On the other hand Multiple unit floating drug delivery system[9] like floating Microballoons, can be distributed widely throughout the gastrointestinal tract[10], providing the possibility of achieving a longer lasting and more reliable release of drug and the Microballoons float over the gastric fluid and not come in contact with the mucus membrane therefore no chance of irritation, the multiple floating system also overcome the problem of all or none related with single unit system[11]. The model drug, Famotidine, is a H_2 antagonist which inhibits many of the isoenzymes of the hepatic CYP450 enzyme system and blocks histamine induced gastric secretion. It is prescribed in conditions like Peptic ulcer, duodenal ulcer, GERD, Zollinger-Ellison Syndrome on a regular basis[12].

In the present study, the effect of the various processing parameters on the size of distribution, yield, incorporation efficiency, In-vitro Buoyancy, In-vitro drug release, along with the bioavailability of Famotidine was investigated.

MATERIALS AND METHODS

Materials

Famotidine obtained as a gift sample from Aristo pharmaceutical Pvt Ltd (M.P. India), was employed as a model drug. Eudragit S100 and Eudragit RSPO (Degussa India Pvt Ltd, Mumbai,India) were used as a polymers, the used organic solvents were Dichloromethane, Ethanol, Isopropyl Alcohol (Merk Ltd, Mumbai, India), Polyvinyl alcohol (Central Drug House, New Delhi, India), functioned as a dispersing agent. All other chemicals / reagents used were of analytical grade.

Method

Floating Microballoons were prepared by the emulsion solvent diffusion method established by Kawashima et al.[13], Famotidine, Eudragit RSPO and Eudragit S100 were dissolved in a mixture of Ethanol, Isopropyl alcohol and Dichloromethane (Table 1).The resulting solution was added slowly to stirring 100 ml aqueous solution of 0.40% (w/v) PVA at 45°C temperature. The stirring was done for 2 hours at 1000-1200 rpm to evaporate the volatile solvent. After evaporation of solvent, Microballoons were collected by filtration, washed with distilled water and dried at room temperature in a desiccator for 24 hours.

Table 1: Formulation code chart of floating Microballoons

Batch	Drug: Polymer ratio			Solvent ratio		
	DRUG	ERSPO	ES100	DCM	ETOH	IPA
FMA1	1	0	1	1	1	1
FMA2	1	0	2	1	1	1
FMA3	1	1	1	1	1	1
FMA4	1	1	2	1	1	1
FMA5	1	2	1	1	1	1
FMA6	1	1	2	2	1	1
FMA7	1	1	2	1	1	0
FMA8	1	2	1	1	1	0
FMA9	1	1	2	3	1	1

Percentage Yield

The prepared Microballoons were collected and weighed. The actual weight of obtained Microballoons divided by the total amount of all non-volatile material that was used for the preparation of the Microballoons multiplied by 100 gives the percentage yield of Microballoons.

Particle Size Analysis

The size of Microballoons was determined by using an optical microscope (Magnus MLX-DX, Olympus, India) fitted with an ocular and stage micrometer. The mean particle size was calculated by measuring 200-300 particles.

Scanning Electron Microscopy

SEM was performed morphological characterization of Microballoons using scanning electron microscope (LEO-430,U.K.). They were mounted directly on to the SEM sample stub using double sided sticking tape and coated with gold palladium film (Thickness 200 nm) under reduced pressure (0.001mmHg).

Estimation of Drug Incorporation Efficiency

To determine the Incorporation Efficiency 50 mg Microballoons were taken and dissolved in 25 ml of 0.1 N Hcl. Then the solution was filtered to separate shell fragments. The estimation of drug was carried out by using a UV Spectrophotometer (Shimadzu UV-1700 series) at the λmax of 266 nm and the Incorporation Efficiency was calculated by the following equation-

$$\text{Incorporation Efficiency} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \times 100 \quad (1)$$

In vitro Buoyancy Study

100 mg of Microballoons were spread over the surface of the dispersing medium (500 ml of 0.1 N Hcl, pH-1.2), at 37°C. The medium was agitated by a paddle rotating at 100 rpm, Microballoons floating on the surface were collected at a predetermined time point, The collected sample was weighed after drying[14]. The percentage of floating Microballoons was calculated by the following Equation –

$$\% \text{ floating ability} = \frac{\text{Weight of floating Microballoons}}{\text{Initial weight of Microballoons}} \times 100 \quad (2)$$

In vitro drug release

The drug release rate from floating Microballoons was determined by using USP XXIII basket type dissolution apparatus. A weighted amount of floating Microballoons equivalent to 20 mg drug was placed in a non-reacting muslin cloth that had a smaller mesh size than that of the Microballoons. The mesh was tied with a nylon thread to avoid the escape of any Microballoons and a glass bead was used in the mesh to induce the sinking of Microballoons. The dissolution test was performed in 900 ml 0.1N Hcl (pH-1.2) at 50 rpm. At specified time intervals, 10 ml aliquots were withdrawn, filtered, diluted with the same medium and assayed at 266 nm for Famotidine using UV Spectrophotometer (Shimadzu UV-1700). Samples withdrawn were replaced with equal volume of the same dissolution medium. All the experiments as specified above were conducted in triplicate.

In-vivo Study

The Institute is approved by Committee for the Purpose of Control and Supervision on Experimental Animals (CPCSEA) with registration no.716/02/a/CPCSEA and my in-vivo work is approved by Institutional Animal Ethics Committee (IAEC) with reference no. BU/PHARM/IAEC/08/013. The in-vivo study conducted in healthy New zealand rabbits weighing 2.0-2.5 Kg. Six rabbits were divided in to two groups and fasted for 24 hour. One batch was fed with 20 mg Famotidine (pure drug), the second batch given the formulation 100 mg (which is equivalent to 20 mg drug). Water was given ad- libitum during fasting and through out the experiment [15].

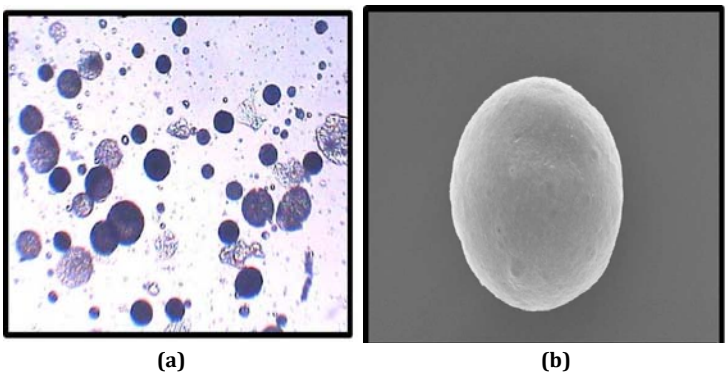
Blood sample, 2 ml each were collected from the marginal ear vein of the rabbits, into heparinized centrifuge tubes just before dosing and at 1, 2, 3, 4, 6, 8, 12, hours during the study. Blood samples were centrifuged at 1500 rpm and the plasma was separated. One undosed plasma sample was kept as a blank. To 1ml of each of the other plasma samples, 5ml of acetonitrile was added, the tubes were then centrifuged at 2500 rpm for 15 min, 4ml of the supernatant was pipetted out to which 0.2ml of 1.47 M perchloric acid was added and the drug concentration was determined by UV Spectroscopy at 258 nm. The blank consisted of 1ml undosed plasma, 4ml acetonitrile and 0.2 ml of 1.47 M perchloric acid [16].

The calibration curve for Famotidine was constructed as follows Famotidine solutions in acetonitrile were prepared at concentration of 1 -10 µg/ml. One milliliter of this solution was made up to 5 ml with using acetonitrile. To each of this solution 1 ml of plasma from undosed rabbit blood was added and content centrifuged at 2500 rpm for 15 minute. Supernatant (4ml) was then pipetted out to which 0.2 ml of 1.47 M perchloric acid was added and the absorbance was measured at 258 nm. The blank was prepared using plasma from the undosed animal, acetonitrile and perchloric acid in exactly the same way. The calibration curve for Famotidine plotted as absorbance at 258 nm versus concentration was liner over the range of 1-10 µg/ml with a correlation coefficient of 0.9991.

RESULT AND DISCUSSION

Morphological Characteristics

The prepared Microballoons showed almost spherical shape and smooth surface.The shape and surface of the Microballoons depend on the amount of Dichloromethane and Isopropyl alcohal, When the large amount of the Dicholomethane used this gave the cracked surface of the Microballoons because of the rapid evaporation of Dichloromethane from emulsion droplets and when large amount of the Isopropyl alcohol used in solvent system, the formed Microballoons were collapsed with each other. This may be due to the slow diffusion rate of the solvent out of emulsion droplet (Fig.1).



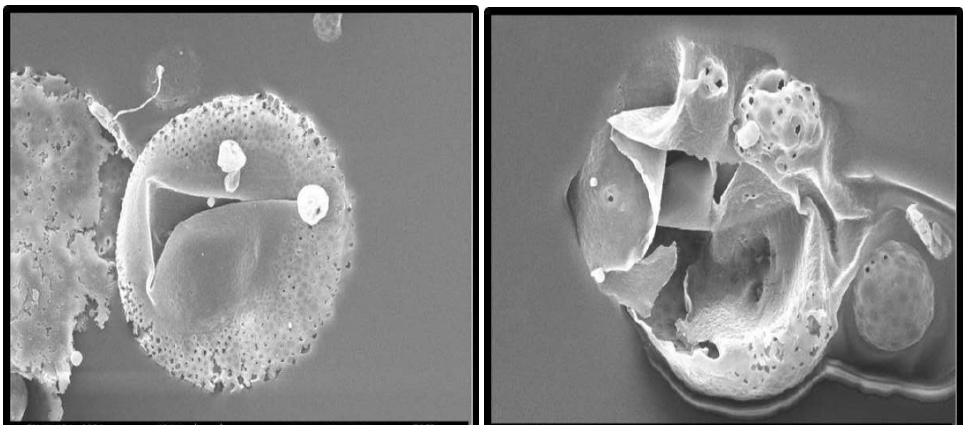
(a) **(b)**

Fig 1: (a) Representation of Microscopic evaluation of floating Microballoons, (b) SEM photograph showing Morphology of batch FMA 6

Scanning Electron Microscopy

SEM micrographs confirmed that prepared Microballoons were spherical with smooth perforated surface (figure 1b).The perforation may be due to evaporation of Dichloromethane form embryonic Microballoon. These images also confirmed that rapid evaporation of Dichloromethane causes rapture of Microballoons .The removal of the two or more adhered Microballoons show a broken surface part on the surface, to avoid such broken part on the surface, the Microballoons should be properly washed with distilled water just after separation to remove PVA, which imparts the adhesion property.

Figure 2b; show the cross section of Microballoon which confirms its hollowness. The morphology of the floating Microballoons was principally depends on the amount of the Dichloromethane and its removal procedure from the emulsion, when the larger amount of the Dicholomethane was used and allowed rapid evaporation of it from the emulsion results in the broken outer surface(Figure 2a).



(a) **(b)**

Fig. 2: (a) SEM Photograph of floating Microballoons showing Hollowness of batch FMA 9, (b) SEM Photograph showing Inner Hollowness of batch FMA6

Mean Particle Size (µm)

The mean particle size of the floating Microballoons ranges from 41.55 ± 4.33 (FMA7) to 73.63 ± 3.68 (FMA9) and it was increased as the amount of the Eudragit S100 increased because the viscosity of the medium increases at the higher polymer concentrations which diminished the shearing efficiency and enhanced the interfacial tension, this result in the formation of the larger size Microballoons. The size of the Microballoons also depend on the amount of the Dichloromethane, the use of higher volume of Dichloromethane gave the larger Microballoons because the Dichloromethane became a major constitutent of internal organic phase due to the preferential diffusion of Ethanol and Isopropyl Alcohol from emulsion droplet and the Eudragit S100 was not soluble at the interface between Dichloromethane and water, started to solidify around Dichloromethane rich emulsion and the volume of the Dichloromethane became a size determining factor thus as the volume of Dichloromethane increased the size of Microballoons also increased (Table 2).

Percentage Yield

The maximum percentage yield was found 88.43 ± 2.83 (FMA5) and the percentage yield was increased as the combination of the Eudragit S100 and Eudragit RSPO was used, instead of the single use of Eudragit S100. This was because the combination of the polymers reduces the probability of formation of aggregates. Thus the percentage yield depends on the properties of the polymers and their respective ratio with the other polymers (Table 2).

In-vitro Floating Ability:-

All the Microballoons showed good floating ability (Figure 3) and the percentage buoyancy was found in the range of 62.86 ± 3.26 (FMA1) to 81.96 ± 1.35 (FMA9), such floating performance was due to insolubility of polymers in the gastric fluid and this was observed that the floating behavior also depend on the amount of Dichloromethane, when higher volume of Dichloromethane was used in the preparation of the formulation that formulation showed the better floating ability than the formulation prepared with the use of lower volume of Dichloromethane, the reason behind this the larger volume of Dichloromethane form the larger air core, which made them lesser dense than gastric fluid, another reason for good floating performance may be the gel forming nature of the polymers in contact of gastric fluid, the air was entrapped by the swollen polymers and that lowers the density of the polymers and confirms buoyancy to the Microballoons (Table 2).

Fig. 3: Floating Property of prepared Famotidine Microballoons in 0.1N Hcl

Table 2: Different Formulation parameters for floating Microballoons

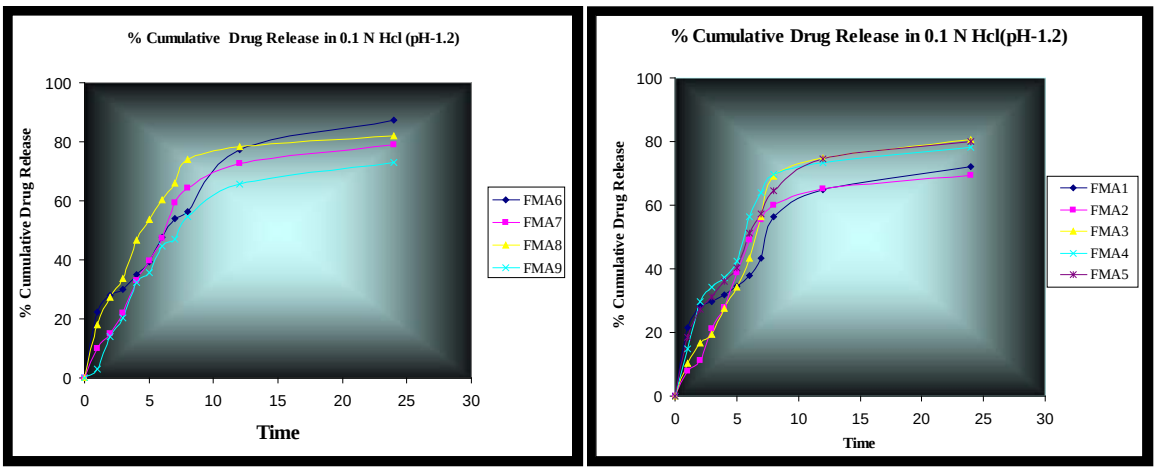
Batch No.	Mean ParticleSize* (µm)	Yield† (%)	Incorporation Efficiency† (%)	Buoyancy† (%)
FMA1	62.33 ± 0.47	65.56 ± 1.32	62.8 ± 4.47	62.86 ± 3.26
FMA2	70.58 ± 1.24	68.50 ± 0.98	65.53 ± 2.05	65.33 ± 2.55
FMA3	50.47 ± 4.62	70.4 ± 2.72	71.94 ± 2.17	68.43 ± 1.20
FMA4	59.66 ± 2.49	74.5 ± 1.72	74.63 ± 1.33	71.10 ± 2.59
FMA5	56.92 ± 1.69	88.43 ± 2.83	63.2 ± 3.26	66.93 ± 1.42
FMA6	55.33 ± 2.05	76.25 ± 0.75	84.43 ± 1.23	80.93 ± 2.31
FMA7	41.55 ± 4.32	83.89 ± 1.12	81.89 ± 0.23	76.36± 0.74
FMA8	63.47 ± 1.81	80.67 ± 2.35	79.13 ± 2.69	70.30 ± 3.89
FMA9	73.63 ± 3.68	74.30 ± 0.64	77.23 ± 3.18	81.96 ± 1.35

* Mean + Standard Deviation, n = 200-300

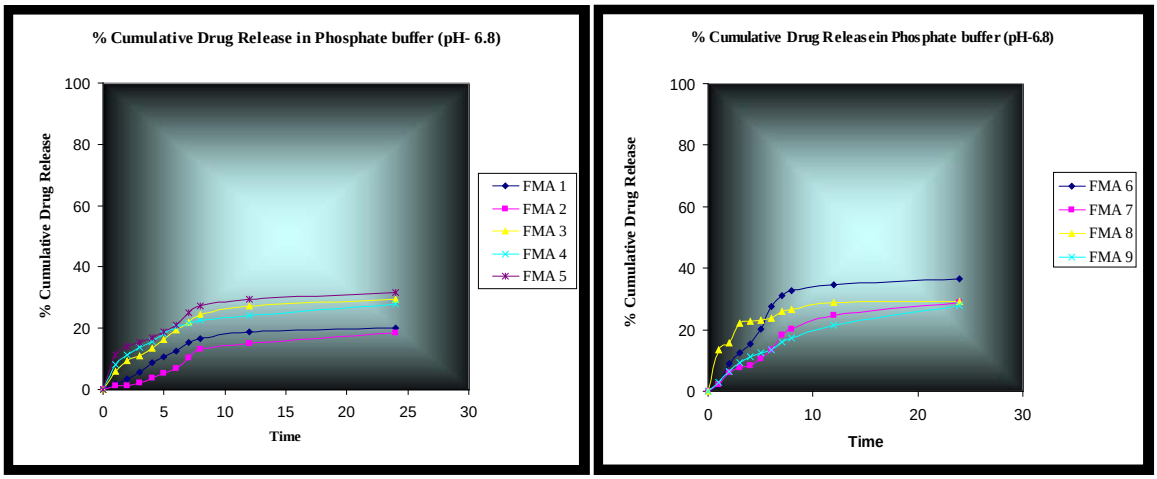
† Mean + Standard Deviation, n = 3

In-vitro Drug Release

The release of Famotidine from floating Microballoons was studied in 0.1N Hcl (pH-1.2) and Phosphate buffer (pH- 6.8). The release of the drug in 0.1 N Hcl (pH-1.2) was more than that of Phosphate buffer (pH-6.8) .This may be due to the drug was soluble in 0.1 N Hcl and the used polymers facilitate the release of drug due to their properties as Eudragit RSPO is pH independent and permeable result in faster release of famotidine in 0.1 N Hcl. The release of Famotidine in Phosphate buffer is less may be due to the poor solubility of drug in Phosphate buffer but the soluble nature of Eudragit S100 at alkaline pH may be responsible for the drug release. This was also observed when the amount of the Eudragit S100 increased, the release of the famotidine from floating Microballoons decreased but when the combination of above with Eudragit RSPO used, increases the release of the Famotidine. This was due to the permeability, swelling and solubilizing nature of the polymers (Figure 4).



(a)



(b)

Fig.4: (a) Percentage cumulative drug release in 0.1 N Hcl (pH-1.2), (b) Percentage cumulative drug release in Phosphate buffer (pH-6.8)

In-vivo Study

The in-vivo evaluation of the floating Microballoons of Famotidine was conducted in two groups of New zealand rabbits. The rabbits has been chosen as the model for study because there have been many bioavailability studies done using this animal model.

Figure 5 shows the graph of blood plasma concentration of the drug vs time for the Famotidine and formulations FMA6, of floating Microballoons. The maximum plasma drug concentration was found at the third hour and then the plasma drug concentration decreases rapidly for the pure drug and shows a "peak and valley" profile of pure drug, but the formulation FMA6 of floating Microballoons showed controlled release kinetic profile. The observed C_{max} ,t_{max} and AUC for the pure drug was 14.99 µg/ml, 3 hour and 44.135 µg h/ml, the C_{max}, t_{max} and AUC for the FMA6 was 12.73 µg/ml, 6 hour, 111.3 µg h/ml, Thus the release of the drug from the formulations FMA6, show the sustained release. The results of the estimation of the area under curve showed that the bioavailability was lesser for the pure drug which was increased with the formulation FMA6.

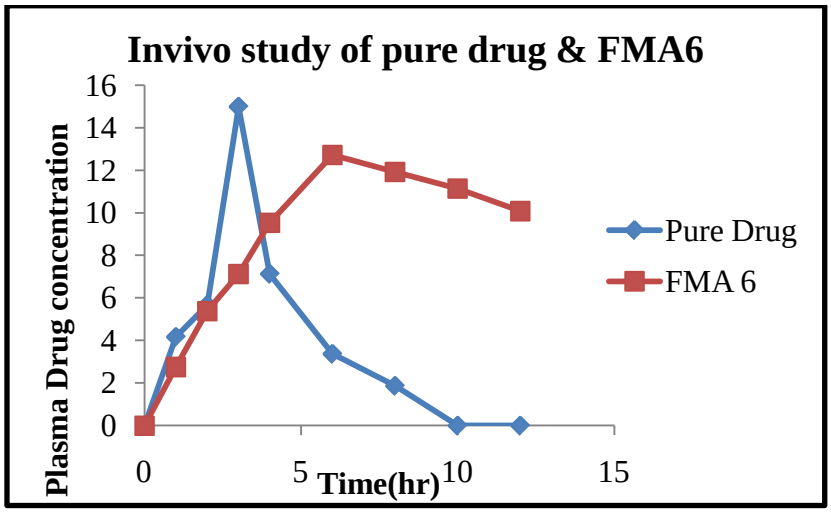


Fig.5: In-vivo bioavailability study of pure drug and formulation FMA6

CONCLUSION

Famotidine Floating Microballoons were prepared successfully and they offer economical, safe and more bioavailable delivery system for effective management of Peptic ulcer and GERD.

ACKNOWLEDGMENT

The authors thank Aristo Pharmaceutical Pvt. Ltd. for a gift sample of Famotidine, Degussa India Pvt. Ltd for a gift sample of Eudragit S100 and Eudragit RSPO.

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