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Instigation and Characterization of Oral Disintegrating Mini-Tablets Containing Salbutamol Sulphate

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ABSTRACT

The Main goal of the present study was to develop and evaluate the orally disintegrating mini-tablets (ODMTs) containing Salbutamol sulphate for the treatment of respiratory disorders like Asthma and Chronic obstructive pulmonary diseases. The problems associated with conventional oral dosage forms are associated with slow down onset of action and lag time, while parenterals and aerosol despite of quick-outset of action strongly affect the patient compliance. Quick release tablets are highly accepted rapid increasing drug delivery systems and thus, an attempt was made to improve the onset of action of drug. To reach this goal, selective superdisintegrants like Crospovidone and Sodium starch glycolate were used in different ratios. Micromeritic properties of the powder were within the limit confirmed by free flowing. ODMTs were compressed in order to have sufficient mechanical strength and integrity to withstand handling, shipping and transportation. The tablets were prepared by direct compression method and physicochemical properties were evaluated. FTIR and DSC studies were confirms no chemical interaction between the excipients and drug. Out of six formulations prepared tablet F3 resulted a least dissolution and disintegration time. Hence, concluded that ODMTs give the better effect to the asthma patients and may serve as a successful strategy for enhancing the bioavailability of drug.

Keywords: Oral disintegrating mini-tablets**,** Salbutamol sulphate, Superdisintegrants, Direct compression method.

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INTRODUCTION

Inspite of tremendous inventive in drug delivery, Solid dosage forms inhabited the enormous and the most important place among all pharmaceutical dosage forms,these route remains desired directions for directing of therapeutic agents because of self- medication, inexpensive therapy, ease of directing, and most importantly patient consent[1].

Tablets are mainly used as solid dosage form, common problems are associated in the tablets like trouble in swallowing and slowdown in the onset of action[2]. Usually among all age groups, 35% of peoples suffering from dysphagia the main drawback of conventional tablet[3].

Oral disintegrating tablets (ODTs) are the new trend dosage form which disintegrates fastly in tongue without need of glass of water and chewing, ODTs also called as "Orodispersible, Fast dissolving, mouth dissolving, porous tablets, rapid dissolving tablet, Crunch- melt tablet, and bite dispersible tablets" these are the few names of the ODTs4.Now days ODTs have most popular dosage form than compared to other pharmaceutical dosage form[5].

Mini-tablets are novel in solid dosage form can be manufactured in a conventional tablet machine. It is possible to produce different kinds of mini-tablets like extended release formulation, gastrointestinal tract, orally disintegrating mini-tablets (ODMTs). In case of higher production rate of capsule instead of filling the capsule usually compressed into mini-tablets[6].

For pediatric patients ODMTs are acceptable more because of the compact size of the tablets. ODMT's as a substitute to conventional oral dosage forms. These dosage forms offers advantages such as accurate dose, improved stability, and better feel mouth compared to liquids. The frequently used formulations in paediatrics are liquid dosage forms it can be smoothly administered to children's. During formulation of liquids the big challenges are the bitter taste of the drug. Other difficulties with liquid dosage forms are bulkiness, reduced stability, and incompatibilities. This problem overcome by mini tablets have been projected as a novel method of oral drug delivery[7].

Asthma is an ordinary respiratory disorder among both children and adults, it is performed usually cause difficulty in breathing, coughing, and cheat pain but in case severe attacks it leads to death[8].

Salbutamol sulphate is a β-2 adrenoceptor agonist used for the treatment of Asthma and Chronic obstructive pulmonary diseases (COPD). The objective of the present study, an attempt is made to develop oral disintegrating mini tablets (ODMT's) of Salbutamol sulphate by simple and cost effective, hence give the better effect to the asthma patients and COPD patients[9].

MATERIALS AND METHOD

Materials

The Material used for preparing ODMTs of Salbutamol sulphate was obtained as gift sample from SM Pharmaceuticals, Bengaluru, Sodium starch glycolate and Crospovidone was obtained from Shreeji chemicals, Mumbai, India. Microcrystalline cellulose obtained from SD fine chemical limited, Mumbai, India. Mannitol, Talc and Magnesium state obtained from SD fine chemical limited, Mumbai, India. Other chemicals used were of analytical grade.

Method

Composition of Oral Disintegrating Mini -Tablets

Orally disintegrating mini-tablets was prepared by using various ratio of superdisintegrants by directly compression method. The superdisintegrants Crospovidone and Sodium starch glycolate was used in various ratios to formulate the orally disintegrating mini-tablets of Salbutamol sulphate. Then powder is compressed into 100mg tablets. The comprehensive organization of the formulation is shown in Table 1.

Table 1: Formulation details of oral disintegrating mini-tablet of salbutamol sulphate

Ingredients (mg\tab)	SSF1	SSF2	SSF3	SSF4	SSF5	SSF6
Salbutamol sulphate	2	2	2	2	2	2
Microcrystalline cellulose	60	60	60	60	60	60
Crospovidone	03	06	09	-	-	-
Mannitol	30	27	24	30	27	24
Sodium starch glycolate	-	-	-	03	06	09
Talc	3	3	3	3	3	3
Magnesium sterate	2	2	2	2	2	2

Preformulation Tests

Angle of repose (θ)

Estimating the flow characteristics of powder sample, it was regulated by funnel method. The dust is poured onto the horizontal surface through funnel, it results the sample freely fall onto the surface. The peak and radius of heap are measured and it was studied by using the formula.

$$\theta = tan - 1(h/r)$$

Apparent density

The total pile of dust split up by the total capacity they occupied. It was regulated by transfer the dust into the measuring cylinder the initial and final volume was noted. Then calculated by using the formula[10].

$$BD = M/V$$

Tapped density

The mass of the powder split up by tapped volume. These blend was poured into measuring cylinder it was tapped, then initial and final volume was noted. Then it was calculated by using the formula

$$TD = M/Vt$$

Carr′s index

It is continuously used is a hint of flowability of a dust and it can be calculated by using the formula.

$$Carr's\ index\ = \frac{TD - BD}{TD} X\ 100$$

Haunser's ratio

It is indication of flowability of the powder blend, it can be defined as tapped density divided by the bulk density. Then it was calculated by using the formula[11].

$$Hausner's\ Ratio\ = \frac{TD}{BD}$$

EVALUTIONS

The Salbutamol sulphate oral disintegrating mini-tablets evaluations for the following parameters

Fourier transforms infra-red spectroscopy (FT-IR) studies

In order to initiate any feasible incompatibility between drug-excipient interaction using FTIR spectrum (FTIR-8400S, Shimadzu, Japan) of pure drug and formulated FDT containing drug were carried out by using spectrum. Scanning range was from 400 to 4000 cm^{-1}. FTIR spectroscopy of samples was obtained by KBr press pellet technique[12].

Differential scanning calorimetric (DSC)

The analysis of pure drug salbutamol sulphate and drug excipients was tested using Shimadzu DSC-60 (PerkinElmer, USA) calorimeter. It was performed at a rate 5.00 ˚C min^{-1} from 10˚C to 300 ˚C temperature range under the nitrogen flow (25ml min^{-1}) finally the DSC thermograms were recorded[13].

^{1}HNMR spectroscopy

^{1}HNMR was done for pure drug and its formulated FDT containing drug were recorded using VNMRS-400 "Agilent-NMR" [14]

Weight variation

The test was carried out by weighing the 10 tablets individually using balance, then comparing the solitary mini-tablet to the average mini-tablet. 10% is the specification of the tablet.

Tablet hardness

From each batch the tablets was measured, by using hardness tester the hardness of the tablet can be determined. Commonly expressed in kg/cm^2**.**

Friability

Twenty mini-tablets was selected from each batch, friabilator is used for the test. The tablets are initially weighed and shifted to friabilator. 25rpm for 4 minutes the drum was rotated, after rotation the tablets was measured by using weighing balance The percentage of friability was calculated by using the formula.

$$\frac{Winitial - WfinalX100}{Winitial}$$

Drug content uniformity

Weighed the 30 mini-tablets then crushed the tablets using mortar and the powder is equivalent to drug. By using buffer the absorbance was noted using UV spectrometer.

***In-vitro* disintegration test**

The conventional disintegration apparatus is used for complete disintegration of mini-tablets. From each batch tablets was introduced into the test apparatus. Determine the time until complete disintegration of each batch, which in turn made it possible to compare the times of disintegration of different batches.

Wetting time test

The tablet is placed on the center of petridish containing water along with dye solution. Then time is noted required to reach the solution completely to upper surface of the tablets [15,16].

***In-vitro* dissolution studies**

In -vitro drug release for the salbutamol sulphate was studied using USP-2 apparatus. The speed of the apparatus was 100 rpm, commonly 37±0.5 ^{0}C water is used. Tablets was introduced to the basket after certain interval the sample was taken and check the absorbance using UV spectrometer[17].

Accelerated stability studies

Stability studies for orally disintegrating mini-tablet of salbutamol sulphate was carried out as per ICH guidelines. Stability studies are conducted for optimized formulations was kept at 40 ± 2^{0}C with 75 ± 5% RH for a period of 3 months. The physical condition and drug content was measured[18]**.**

RESULTS AND DISCUSSION

Orally disintegrating mini-tablet (ODMTs) of Salbutamol sulphate was prepared using various ratios of super disintegrants by compression method. The superdisintegrants Crospovidone and

Sodium starch glycolate were used in various concentrations (3%, 6% and 9%) to formulate the ODMTs of Salbutamol sulphate.

Evaluation parameters

Pre –formulation studies of ODMTs

Micromeritic properties of the prepared mini-tablets of all the batches of powder are recorded in the Table 2

Table 2: Pre formulation studies of powder blend

Code	Angle of repose (°) (±SD*),	Apparent density(g/cc) (±SD*),	Tapped density(g/cc) (±SD*)	Carr's index (%) (±SD*)	Haunser's ratio (±SD*)
SSF1	25.98±0.021	0.426±0.0015	0.616±0.0068	19.28±0.075	1.32±0.045
SSF2	25.95±0.020	0.4486±0.0041	0.616±0.0152	18.85±0.020	1.35±0.046
SSF3	25.85±0.01	0.4142±0.0010	0.61±0.01	15.33±0.01	1.3±0.02
SSF4	29.52±0.068	0.457±0.0060	0.666±0.0152	15.48±0.101	1.33±0.043
SSF5	28.20±0.095	0.4486±0.0075	0.65±0.01	18.4±0.1	1.32±0.026
SSF6	29.87±0.02	0.4593±0.0081	0.66±0.01	19.23±0.057	1.31±0.045

***Standard deviation, n=3**

The data obtained for the apparent density and tapped density for the all the batches in the particular range of 0.4142±0.001 to0.459±0.008 g/cc and 0.6±0.006-0.66±0.01g/cc. and angle of repose was obtained for all the batches 25.85˚C ±0.01 to 29.87˚C ±0.02implies that powder have passable flow properties, respectively Carr's index values was found in the range of 15.33±0.01 to19.28±0.07% which indicates that have good compressibility. Haunser's ratio values obtained was in the particular range of 1.3±0.02 to1.35±0.046 which shows the passable flow property according to USP as reported in Table 2

Fourier Transformed Infrared (FT-IR) Studies

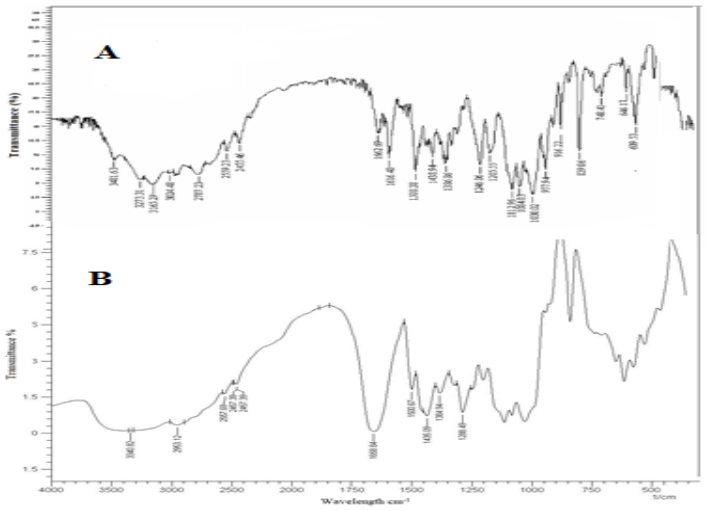

Figure 1: FT-IR spectrum of pure drug (A) and Formulated FDT containing drug (B).

IR spectroscopic studies of pure drug Salbutamol sulphate and formulated FDT containing drug was performed and FTIR spectra of Salbutamol sulphate showed leading peak at divergent wavenumber corresponding its functional group, it confirms that pure drug as per established standards. They exhibited peak at 3165.29 cm^{-1}, 2787.23cm^{-1}, 1386.86cm^{-1}, 1508.38cm^{-1}, 1084.03 cm^{-1}, 839.06cm^{-1},(OH Stretching, Aliphatic CH Stretching, Aliphatic CH Bending, C=C Stretching, C-O Stretching, Aromatic CH Bending). The IR spectra of formulated FDT containing drug showed the characteristic absorption bands at 3340.82cm^{-1}, 2953.12cm^{-1}, 1384.94cm^{-1}, 1500.67cm^{-1}, 1101.12cm^{-1}, 839.06cm^{-1},(OH Stretching, Aliphatic CH Stretching, Aliphatic CH Bending, C=C Stretching, C-O Stretching, Aromatic CH Bending). From this study observed that on comparing spectrum all the characteristic peaks of Salbutamol sulphate were present in all the spectrums thus indicating compatibility between drug and other excipients and it can be concluded that the characteristics bands of Salbutamol sulphate were not affected in presence of other excipients. It shows that there was no significant change in the chemical integrity of the drug and excipients.

Differential scanning calorimetry (DSC)

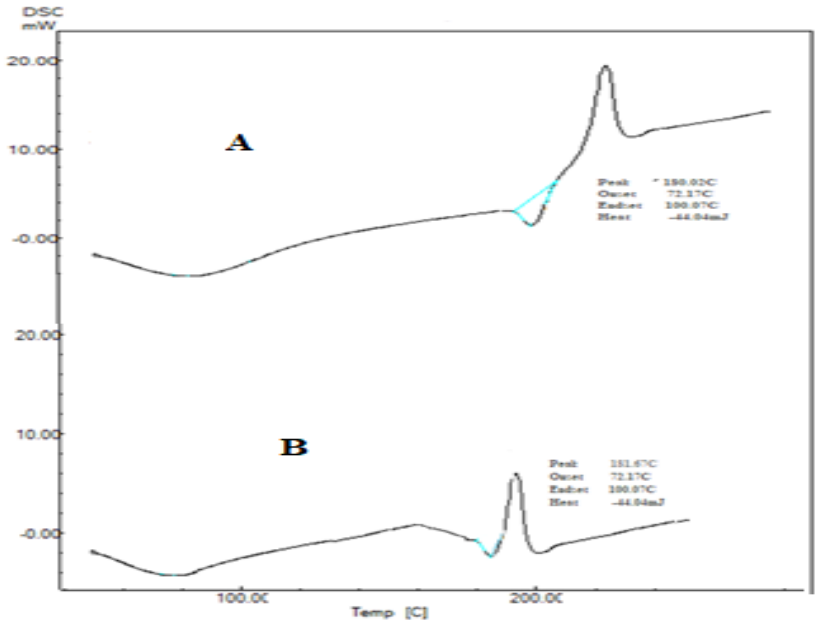

Figure 2: DSC of salbutamol sulphate (A) and Formulated FDT containing drug (B)

DSC studies of the Salbutamol sulphate was carried out for the pure drug and the physical mixture (Salbutamol sulphate+ Crospovidone+ Sodium starch glycolate) using shimadzu DSC-60 colorimeter at the rate 5.00 ˚C min^{-1} from 10˚C to 300 ˚C temperature range under nitrogen flow of 25ml min^{-1}. The endothermic peak of pure drug at 180.02℃ which slightly more than its melting point, indicating the crystallinity.The physical mixture show the endothermic peak at 181.56 ℃.

Indicates that there is no interaction between the polymers and drug is compatible with all the excipients.

Evaluation parameter of post formulations

Evaluation parameters orally disintegrating mini-tablet of salbutamol sulphate were recorded in the Table-3

Table 3: Evaluation parameter of Salbutamol sulphate ODMT

Code	Hardness (Kg/cm^2) (±SD*)	Friability (%) (±SD$^{\alpha}$)	Weight variation (mg) (n±SD$^{\alpha}$)	Wetting time (sec) (±SD$^{\beta}$)	Disintegration time (sec) (±SD$^{\beta}$)	Drug content uniformity (%) (±SD*)
SSF1	1.93±0.152	0.361±0.028	100.17±0.6360	5.52±0.13	19.5±0.5	97.83±0.09
SSF2	2.13±0.153	0.415±0.020	100.1±1.007	4.10±0.06	15.5±0.51	95.67±0.10
SSF3	1.76±0.151	0.34±0.02748	100.02±0.250	2.68±0.01	13.3±0.65	98.65±0.15
SSF4	1.9±0.1	0.356±0.0287	101.39±1.531	10.5±0.08	38.43±0.7	94.82±0.06
SSF5	1.85±0.06	0.361±0.028	101.45±1.550	7±0.1	24.93±0.4	94.55±0.06
SSF6	1.923±0.07	0.427±0.0115	101.49±1.5293	20.6±0.01	51.1±0.4	93.67±0.05

***Standard deviation=3, $^{\alpha}$Standard deviation, n=10, $^{\beta}$Standard deviation, n=6,**

Hardness of the tablet was found in the range 1.76±0.151 to 2.13±0.153 hence concluded tablets were having good mechanical strength. Friability test of the tablet values for all the batches was in the particular range 0.34±0.02748 to 0.427±0.0115(less than 1%) hence formulations shows compressed in order to have sufficient mechanical strength and integrity to withstand handling, shipping and transportation. According to USP the tablets from each batch passed the weight variation was found in the range 100.02±0.250 to 101.49±1.5293within the specification of the USP limits (±7). Drug content of the tablet was found in the range 93.67±0.058 to 98.65±0.150, it was within the limits indicating that to prepare the powder blend and tablets distributed the uniformity of the drug throughout the blend. Wetting time is closely related to the inner structure the tablet was found in the range 2.68±0.01 to 10.5±0.081.According to USP the formulations should disintegrate completely within one minute which shows faster disintegration. Hence immediate disintegration may be due to the immediate uptake of the medium, swelling and thereby increasing bioavailability of the drug.

^{1}HNMR:

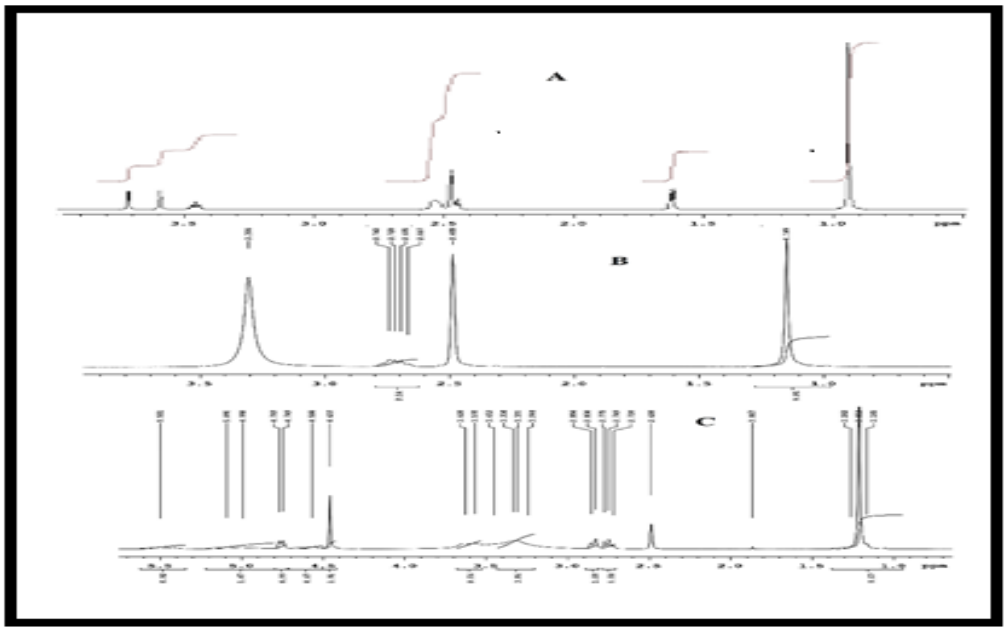

Figure 3:^{1}HNMR of Salbutamol sulphate (A) and Formulated FDT containing drug (B)(C).

^{1}HNMR studies related to the functional group involved in the Complexation and the chemical shift values in ^{1}HNMR depict the mechanism of Complexation. The structural elucidation using ^{1}HNMR showed that the Salbutamol and physical mixtures are compatible with each other. These result confirmed that the drug and excipient does not have interaction between them.

Comparative *in-vitro* drug release

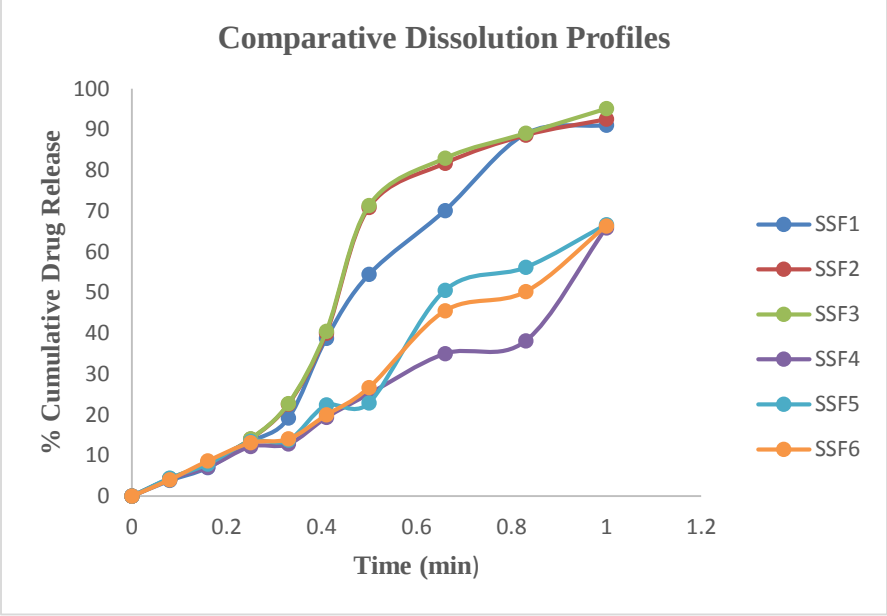

Figure 4: Comparative *in-vitro* drug release profile of Salbutamol sulphate for formulations SSF1 to SSF6

The *in-vitro* drug release profile for all the batches (SSF1 to SSF6). The formulations showed an average range bi-phasic drug release at the end of 6 minutes. Figure illustrates the comparative in-

vitro drug release profile for Salbutamol sulphate for formulations SSF1 to SSF6. It was observed that only the formulations with Crospovidone (SSF1, SSF2, and SSF3) took the shortest time to release more than 90% of the drug at the end of 1 minute.

Stability studies

Table 4: Accelerated stability studies of F3 formulation of Salbutamol sulphate

Temperature and RH	Parameters	Duration in months			
		0	1	2	3
40±2˚C and 75±5%	Wetting time	2.68	2.65	2.60	2.50
	Disintegration time	13.3	13.0	12.9	12.2
	%Drug content	98.65	98.45	98.27	97.98
	%CDR	95.48	95.35	95.21	94.96

For optimized formulation stability studies was performed at temperature 40±2˚C (Oven) and 75±5% (Ambient humidity) as per ICH guidelines for a period of 3 months. After performing stability studies it was observed that at stability testing conditions there was negligible change in the wetting time, disintegrating time, drug content and cumulative drug release of formulation SSF3 when compared to initial values. From this study we can conclude that the developed formulations SSF3 will be revealed that physicochemically stable throughout their stability period.

CONCLUSION

It concluded that oral disintegrating mini-tablet containing Salbutamol sulphate formulated by compressed direct method by using superdisintegrants such as Sodium starch glycolate and Crospovidone in different ratios. All the prepared formulation were found to exist in acceptable limits. Among the formulations the superdisintegrant Crospovidone showed the better result compared with Sodium starch glycolate where increase dissolution and disintegration time there seen and the optimized formulation (SSF3) showed the improved versatility and better patient compliance. Hence the ODMTs which are prepared shows the better effect to the asthma disease.

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