Original Article

FORMULATION AND EVALUATION OF CAPTOPRIL GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM

*Vijayasankar G R[1], Naveen Kumar Jakki S[2], Suresh AG[2], Packialakshmi M[3]
[1]*Vishwa Bharathi college of Pharmaceutical Sciences, Guntur, Andhrapradesh, India-522009.*
[2]*Santhiram college of Pharmacy, Nandyal, Andhrapradesh, India-518112.*
[3]Schaavan college of Pharmacy, Nellore, *Andhrapradesh, India*- 524003.

Abstract
The present study is the most feasible approach to control the gastric residence time using gastroretentive dosage forms with required efficacy, safety and stability of the drug. Three different grades of Hydroxypropyl Methyl cellulose, Lactose, Sodium bicarbonate and Magnesium stearate were used as a variant with Captopril as active pharmaceutical ingredient. The tablets were prepared by direct compression method. Differential Scanning Calorimetry (DSC) studies showed that no polymorphic changes occurred during manufacturing of tablets. Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias. Results of *in vitro* release profile indicated that formulation (F5) was the most promising formulation as the extent of drug release from this formulation was high as compared to other formulations. Results of in-vitro swelling study indicate that the formulation F5 was having considerable swelling index. From the in vitro buoyancy studies, it was found that almost all the batches containing effervescent agent showed immediate floatation followed by floatation period of more than 8h. It was concluded that the tablets of batch F5 had considerable swelling behaviors and *in vitro* drug release. It was observed that tablets of batch F5 followed the Higuchi modal release profiles. From the results obtained, it was concluded that the formulation F5 is the best formulations as the extent of drug release was found to be around 96.22 % at the desired time 8hour. This batch also showed immediate floatation and floatation duration of more than 8hour.

Keywords: Captopril, Hydroxypropyl methyl cellulose, Gastroretentive oral controlled.

Introduction
Oral controlled release delivery systems are programmed to deliver the drug in predictable time frame that will increase the efficacy and minimize the adverse effects and increase the bioavailability of drugs. Oral drug delivery is most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form [1]. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process [2]. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

**** Author for Correspondence:***

G R Vijayasankar,M.Pharm
Dept. of Pharmaceutics,
Vishwa Bharathi college of Pharmaceutical Sciences,
Guntur, Andhrapradesh, India-522009.
Email: gmjv@rediffmail.com

Captopril belongs to class Angiotensin Converting Enzyme inhibitor (ACE inhibitor). It affects the rennin-Angiotensin system and inhibits the conversion of relatively inactive Angiotensin I to active Angiotensin II. ACE inhibition increase bradykinin synthesis which stimulate prostaglandin biosynthesis. Bradykinin and prostaglandin contribute pharmacological effect of ACE inhibitor all these effects produces vasodilatation. Captopril after oral dose produces antihypertensive action for the period of 6 – 8 h, it requires a daily dose of 37.5–75 mg to be taken three times, most stable at pH 1.2 and as the pH increases becomes unstable and undergoes a degradation reaction. These two drawbacks can be overcome by developing a floating dosage form to be remained buoyant in the stomach. Floating drug delivery system increases the gastric residence time, stability, patient's compliance and sustains the release of the drug hence increases the bioavailability.

Materials and Methods
Captopril and was obtained as a generous gift by Modi-Mundipharma Private Ltd. Hydroxypropyl methyl cellulose K4M (HPMC K4M) purchased from Central Drug House (P) Ltd. India. HPMC K15M and HPMC K100M from Colorcon, Mumbai, India. Spray dried lactose from Vardhman Healthcare, Mullana, India. Magnesium stearate and Sodium bicarbonate were purchased from Qualigens Fine Chemicals, Mumbai, India. Other reagents used are analytical grade.

Formulation of Floating Tablets

Table 1: Formulation of Captopril with three different HPMC grades

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Captopril	25	25	25	25	25	25	25	25	25
HPMC K4M	60		-	100	-	-	50	-	50
HPMC K15M	-	60			100	-	50	50	-
HPMC K100M	-	-	60			100	-	50	50
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20
Lactose	94	94	94	64	64	64	64	64	64
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total	200	200	200	200	200	200	200	200	200

Captopril was used with various grades of HPMC in varying ratios to formulate the floating tablets. The floating matrix tablets were prepared by mixing drug, lactose, Magnesium stearate and HPMC geometrically in a pestle and mortar until homogenized. All the ingredients were passed through sieve - 80 before processing sodium Bicarbonate is added. The mixture was directly compressed in a R&D tablet compressing machine fitted with flat punches and dies (8 mm diameter). The tablet weight was adjusted to 200mg and 25 tablets for each batch were prepared.

Tablet Hardness

The crushing strength Kg/cm^2 of prepared tablets was determined for 10 tablets of each batch by using Monsanto tablet hardness tester [3]. The average hardness and standard deviation was determined. The results are shown in Table 3.

Uniformity of Weight

Twenty tablets were individually weighed and the average weight was calculated. From the average weight of the prepared tablets, the standard deviation was determined. The results are shown in Table 3

Friability

Twenty tablets were weighed and placed in the Electrolab friabilator and apparatus was rotated at 25rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again.

Uniformity of Content

Five randomly selected tablets were weighed and powdered. The powdered tablet equivalent to 20 mg drug in one tablet was taken and transferred in a 250ml flask containing 100ml of 0.1N HCl (pH 1.2). The flask was shaken on a flask shaker for 24 hours and was kept for 12 hours for the sedimentation of undissolved materials. The solution is filtered through Whatman filter paper. 10ml of this filtrate was taken and appropriate dilution was made. The samples were analyzed at 202 nm using UV visible spectrophotometer.

In Vitro Buoyancy Test

The prepared tablets were subjected to *in vitro* buoyancy test by placing them in 250 ml beaker containing 200ml 0.1 N HCl (pH 1.2, temp. 37±0.5 °C). The time between introduction of the dosage form and its buoyancy in the medium and the floating durations of tablets was calculated for the determination of lag time and total buoyancy time by visual observation. The Time taken for dosage form to emerge on surface of medium called Floating Lag Time or Buoyancy Lag Time and total duration of time by which dosage form remain buoyant is called Total Floating Time [4].

Swelling index

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of weight gain by the tablet [5].

Each tablet from all formulations pre-weighed and allowed to equilibrate with 0.1N HCl (pH-1.2) for 5h, was then removed, blotted using tissue paper and weighed [6]. The swelling index was then calculated using the formula:

$$\text{Swelling index WU} = \frac{(W_1 - W_0)}{W_0} \times 100$$

Where, W_t = Weight of tablet at time t.

W_0 = Initial weight of tablet

In vitro Dissolution Study

In Vitro dissolution study was carried out using USP II apparatus in 900 ml of 0.1 N HCl (pH 1.2) for 8 hours. The temperature of the dissolution medium was kept at 37± 0.5°C and the paddle was set at 50 rpm. 10 ml of sample solution was withdrawn at specified interval of time and filtered through Whatman filter paper. The absorbance of the withdrawn samples was measured at λ_{max} 202 nm using UV visible spectrophotometer [7, 8].

Modeling of Dissolution Profiles

In the present study, data of the *in vitro* release were fitted to different equations and kinetic models to explain the release kinetics of Captopril from the floating tablets. The kinetic models used were a Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models [9, 10].

Zero Order Kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation;

$$Q_t = Q_o + k_o t$$

Where, Q_t = amount of drug released in time't',

Q_o = initial amount of drug in the solution,

k_t = zero order release constant.

First Order Kinetics

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967). The following relation can express this model:

$$\text{Log } Q_t = \text{Log } Q_o + k_t t/2.303$$

Where, Q_t = amount of drug released in time 't'; Q_o = initial amount of drug in the solution, k_t = first order release constant.

Higuchi Model

Higuchi (1961, 1963) developed several theoretical models to study the release of water soluble drugs incorporated in semisolid and/or solid matrixes. Simplified Higuchi model can be expressed by following equation:

$$f_t = k_H t^{1/2}$$

Where, k_H = Higuchi diffusion constant, f_t = fraction of drug dissolved in time't'.

Korsmeyer-Peppas Model

Korsmeyer et al., (1983) developed a simple, semiempirical model, relating exponentially the drug release to the elapsed time (t);

$$f_t = at^n$$

Where, **a** = constant incorporating structural and geometric characteristics of the drug dosage form, **n** = release exponent, $f_t = M_t/M_\infty$ = fraction release of drug.

Stability Studies

The mixture of drug and the excipients and three tablets of each formulation were placed in humidity chamber at, 40^{0}C, and 2-8^{0}C for 30 days. After the completion of one month the samples were analyzed visually for any color changes due to physical and chemical interaction within excipients and with the drug. The percentage drug content in all the tablets was determined after specified period [11, 12].

Result and Discussion

Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimetry studies were carried out to study the changes in amorphous to crystalline or vice-versa or any polymorphic changes during formulation of tablets. Differential Scanning Calorimetry studies revealed that there were no polymorphic changes in drug as well as excipients during manufacturing of tablets.

Evaluation of Granules

Table 2:

Pre-compression parameters of Formulation F1-F9

Parameters / Batch No.	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F1	0.521	0.585	10.34	1.12	22^0
F2	0.533	0.597	10.16	1.13	24^0
F3	0.562	0.611	8.19	1.08	21^0
F4	0.543	0.583	6.89	1.06	21^0
F5	0.582	0.661	9.37	1.13	24^0
F6	0.566	0.613	8.19	1.08	21^0
F7	0.544	0.593	8.19	1.09	20^0
F8	0.580	0.633	7.93	1.07	22^0
F9	0.591	0.642	7.90	1.08	22^0

Evaluation of Tablets

Table 3:

Post-compression parameters of Formulations F1-F9

Parameters / Batch No.	Weight variation	Hardness (kg/cm2)	Friability (%)	Drug Content (%)
F1	Pass	5.6	0.51	98.5
F2	Pass	5.9	0.63	99.1
F3	Pass	6.2	0.69	98.1
F4	Pass	6.0	0.58	99.4
F5	Pass	6.4	0.69	99.5
F6	Pass	6.9	0.72	96.2
F7	Pass	7.2	0.53	97.3
F8	Pass	7.4	0.49	98.4
F9	Pass	7.6	0.41	99.2

(n=3, the data represents the mean of three observations**)**

In vitro Buoyancy Studies

Table 4: Invitro Buoyancy study of formulations F1-F9

Batch	Buoyancy Lag Time(sec.)	Total Floatation time(hr.)
F1	100	8
F2	115	8
F3	180	8
F4	105	8
F5	120	>12
F6	155	>12
F7	165	>12
F8	170	>12
F9	180	>12

***In* Vitro Dissolution Studies**

In vitro dissolution studies of the prepared floating/ non-floating matrix tablets of Captopril was carried out on USP-II dissolution apparatus using paddle. Absorbance for the sample withdrawn was recorded and percent (%) drug release at different time intervals are shown in table no. 5 Comparison between different Batches for *invitro* dissolution showed in figure no 1-3.

Table 5: Cumulative percentage release for the formulation F1 – F9

Time (min)	Cumulative % release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
30.000	30.43	29.67	23.10	26.05	25.29	21.78	32.62	20.69	28.90
60.000	45.13	47.63	40.74	42.51	40.54	32.89	41.67	25.95	37.93
120.000	58.93	54.89	49.38	57.38	56.17	39.16	54.86	36.93	45.53
180.000	69.85	63.37	54.79	73.56	63.37	43.90	60.30	43.89	51.60
240.000	83.16	76.88	59.64	81.75	76.88	49.29	67.23	52.68	59.19
300.000	97.46	84.18	65.80	88.15	81.88	56.55	75.70	59.74	67.33
360.000	-	90.79	69.45	93.99	89.25	60.42	82.64	65.91	80.08
420.000	-	92.34	76.91	96.95	93.01	66.13	90.45	70.98	88.14
480.000	-	95.10	79.91	-	96.22	72.08	92.93	76.92	91.82

Table 6:
Swelling Index of Tablets of Batches F1 to F9

Batch	TIME (HRS)					
	0	1	2	3	4	5
F1	0	41.25	54.48	65.32	70.05	88.12
F2	0	49.25	61.54	72.90	82.37	92.54
F3	0	35.21	48.92	55.76	69.52	78.2
F4	0	36.09	47.45	55.32	67.12	78.97
F5	0	45.73	59.76	67.72	81.26	91.60
F6	0	32.55	43.35	57.32	62.45	74.09
F7	0	36.76	48.98	59.54	67.06	81.78
F8	0	28.45	42.78	53.87	61.58	75.02
F9	0	43.06	57.96	65.32	78.34	92.09

Comparison of Different Formulations

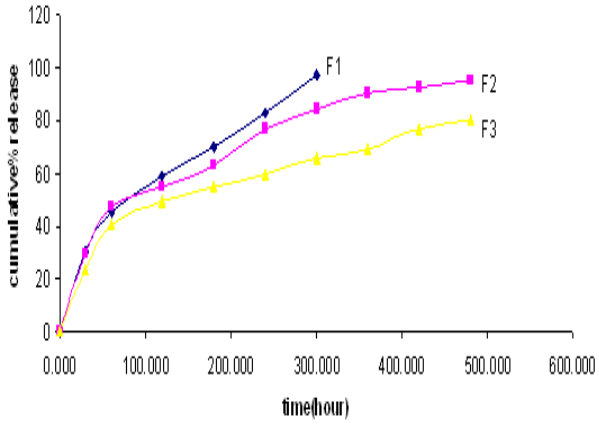


Figure 1
Comparative release profiles of F1, F2 and F3

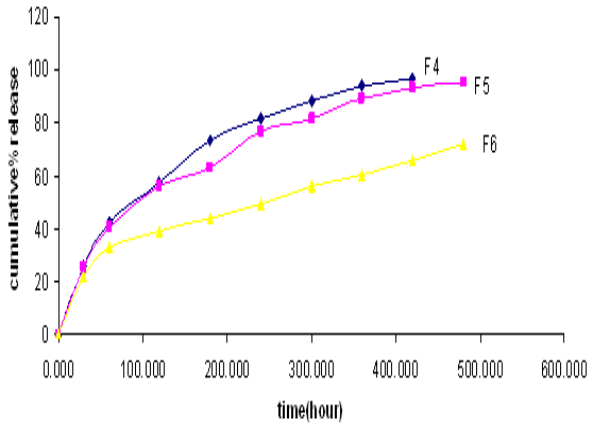


Figure 2
Comparative release profiles of F4, F5 and F6

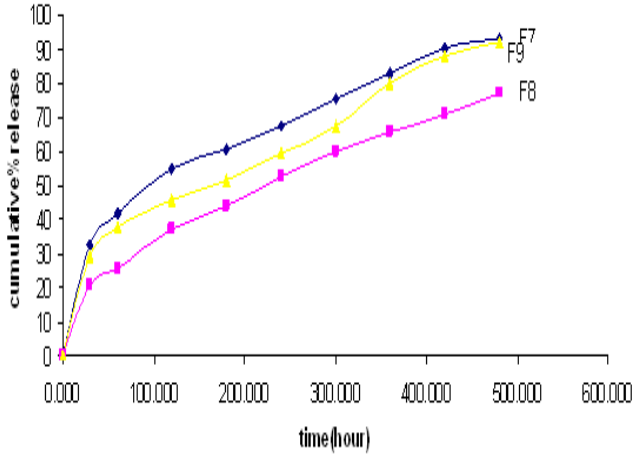


Figure 3
Comparative release profiles of F7, F8 and F9

Effect of HPMC Concentration on Drug Release

The batches F1 to F9 were prepared using polymers HPMC K4M, K15M, and K100M respectively and the polymer concentration in the batches was taken to be 30%-50%and combination of these polymers. Effervescent tablets were prepared for each batch and concentration of effervescent agent was taken to be 10% of the total tablet weight. The drug release rate decreased in the rank order K4M> K15M > K100M. This can probably be attributed to the different diffusion and swelling behavior in/of these polymers. With increasing molecular weight, the degree of entanglement of polymer chain increases. Thus, the mobility of the drug molecules in the fully swollen systems decreases. This leads to decreased drug diffusion coefficients and decreased drug release rate with increase molecular weight. It is stated that a faster and greater drug release was expected for reasons with the evolution of gas, the matrix would become more relaxed allowing water penetration and diffusion of drug might be easier.

The tablets of the batches F1-F6 were prepared by using HPMC K4M, K15M, and K100M respectively. The tablets of batches F7 to F9 were prepared with the combination of three polymers. The tablets with different concentration (30&50%of polymer respectively) were prepared in these batches. The percentage of drug released decreased with increasing the polymer concentration and molecular weight

It is observed from the data that the dissolution rate also decreases with decrease in drug release as the molecular weight and concentration of polymer is increased. All the tablets of these batches degraded by surface erosion and eroded to a large extent at the end of the study but did not disaggregate.

From the above observation it is concluded that formulation F5 (HPMC-K15 50%) is the best formulation among all other

formulations because it is showing very controlled release of drug from Tablet formulations.

***In vitro* Buoyancy**

On contact with the water the dissolution medium, hydrochloride in the test medium reacted with sodium bicarbonate in the matrix inducing CO_2 formation in the floating section, there by decreasing the density of the matrix system and aid in floatation. Because of the gas generated in trapped in and protected by the gel formed by hydration of HPMC, the expansion of the floating section keeps the whole tablet buoyant on the surface of the test medium.

There was an increase in the floatation lag time which could be attributed to the fact that tablets containing low viscosity HPMC swell rapidly than tablets with high viscosity HPMC. Also higher floatation time of these tablets could be explained by a slower CO_2 formation because of the presence of the effervescent agents within the HPMC matrix. Medium can penetrate these tablets easily and react with Sodium bicarbonate to liberate CO_2. It is because the buoyancy force build up due to the entrapment of CO_2 is strong enough for the whole tablet to go up to the surface and maintain the tablet on the surface for as long as 8h. Tablets of all batches remained floatable throughout the study.

The optimized batch is showing Buoyancy lag time (120 sec.) and its total Floatation time is more than 12 h (Table 4)

Modeling

The data obtained from dissolution studies of different batches was analyzed using different mathematical model for the determination of release kinetics. The kinetic models used were zero order, first order, Higuchi model and Korsmeyer-Peppas model. For batches F5, the best fit model with the highest correlation was shown by both Higuchi model (r^2 = 0.9935) and followed by Korsemeyer peppas (r^2 = 0.9698)

Fig.4: DSC Curve of Pure Drug

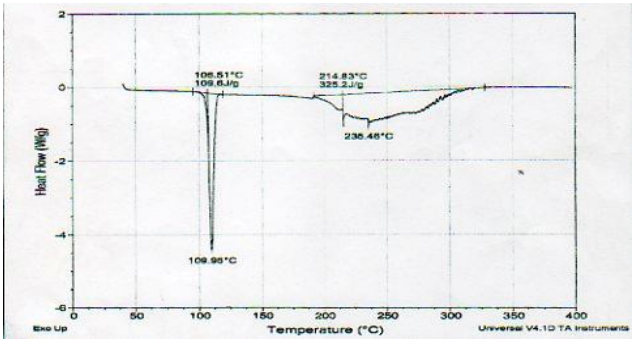


Fig.5: DSC Curve of HPMC K4M

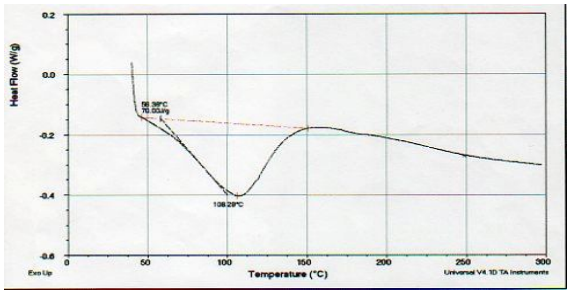


Fig.6: DSC Curve of HPMC K15M

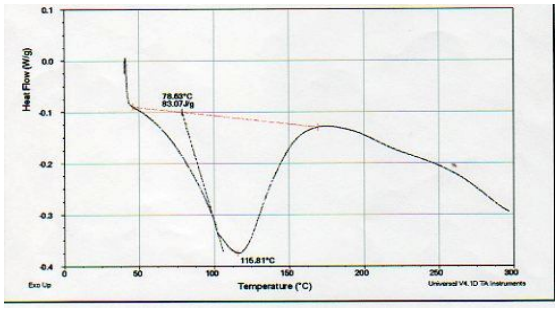


Figure 7: DSC Curve of HPMCK100M

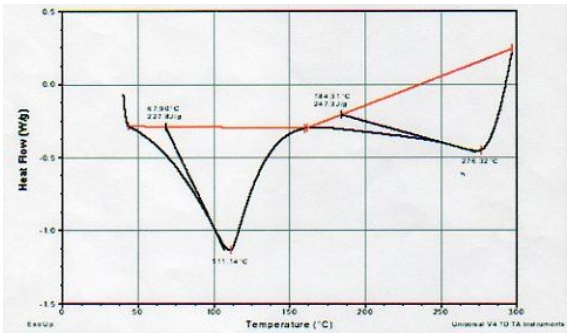


Figure 8: DSC Curve of Lactose

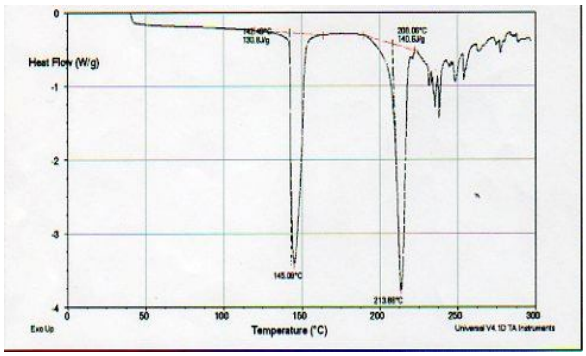
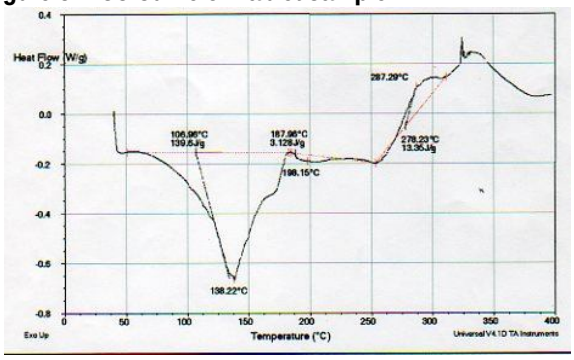


Figure 9: DSC Curve of Tablet Sample



Stability studies

Stability study was carried out for one month on mixture of drug with excipients and the prepared tablets formulation. After one month the samples were analyzed for the changes in physical appearance and drug content. No change in the physical appearance of the mixtures and the tablets was found.

Conclusion

From the results and inference we can certainly say that floating type gastroretentive drug delivery system holds a lot of potential for drug having stability problem in alkaline pH or which mainly absorb in acidic pH. We can certainly explore this drug delivery which may lead to improved bioavailability and ensured therapy with many existing drugs. It is the responsibility of future scientists working in this area to effectively use the potential of this drug delivery system for the benefit of mankind.

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