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Research Article

Formulation and Evaluation of Sustained Release Matrix Tablet of Metformin Hydrochloride.

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ABSTRACT

Attempt was to formulate the oral sustained release metformin hydrochloride matrix tablets by using hydroxypropyl methylcellulose of (HPMC K-50 M).The tablets were prepared by wet granulation technique. The granules were evaluated for angle of repose, loose bulk density, tapped and bulk density. It shows satisfactory results. The tablets were subjected to thickness, weight variation, drug content, hardness, friability, and *in-vitro* release studies. *In-vitro* dissolution profiles of the all formulations were studied in 0.1 N HCl for first 2 hours then 6.8 pH phosphate buffer for next 10 hours using USP dissolution apparatus II (paddle) apparatus. FTIR spectral studies showed that there was no interaction between the drug and excipients. In development of Metformin HCl sustained release tablets was a good approach to sustain the release rate to overcome frequent administration and also to release the drug for a prolong time.

KEYWORDS

HPMC K50, factorial Design, FTIR, DSC, *In-Vitro* Dissolution.

1. INTRODUCTION

Oral drug delivery is preferred route of administration for most of the active drug molecules due to its several advantages like greater flexibility in design and high patient compliance. Because of greater stability, accuracy in dose, easy of production, formulation of tablets is preferred oral dosage form. Tablet availability in market range from relatively simple immediate-release (IR) formulation to complex sustained release (SR) or modified release dosage forms[1].Sustained release drug delivery system was aimed to release the medication in a prolonged rate to maintain plasma drug levels. The drugs having shorter half life are suitable for the sustained drug delivery system. The main objective in designing sustained delivery system is to reduce dosing frequency and thereby increasing the action[2]. The drug molecules shows better sustained drug release profile in matrix systems by different mechanisms[3]. Metformin hydrochloride is an orally administered biguanide, widely used in the management of type-2 diabetes, a common disease that combines defects of both insulin secretion and insulin action[6]. It is a hydrophilic drug which slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability is reported to be of 50 - 60% has relatively short biological half life of 1.5 - 4.5 hours. However, frequent dosing schedule and risk of gastrointestinal symptoms make its dose optimization complicated. Thus, it is reasonable to assume the requirement of sustained release metformin formulation to prolong its duration of action and to improve patient compliance[4].

In the present study Metformin HCl sustained release tablets were prepared by wet granulation method using natural and synthetic polymers in varying concentrations.

2. MATERIALS AND METHODS

2.1. Materials

HPMC K-50 was purchased from Milan laboratory Mumbai; Metformin HCl,PVPK-30, Microcrystalline cellulose, Maize starch, Magnesium Stearate and talc obtained as gift samples from Sohan healthcare Pvt. LTD Kurkumbh, Daund, Pune. All the ingredients used were of analytical grade.

2.2. Formulation of Metformin HCl Sustained Release (SR) Tablets

2.2.1. Drug-polymer physical interaction study

Infrared spectrum was taken by scanning the samples of pure drug and the polymers individually over a wave number range of 4000 to 400cm–1 using Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan). The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer.

DSC study of untreated and spray-dried metformin hydrochloride samples were carried out on a differential scanning calorimeter (Shimadzu, Japan). Samples, of 2 mg each, of untreated drug and spray-dried powder of the optimized batch were held for 1 minute at 50°C and then heated gradually at 10°C min–1 in crimped aluminum pans under a nitrogen atmosphere from 50 to 270°C. The onsets of melting points and enthalpies of fusion of samples were automatically calculated by the instrument.

2.2.2. Preparation of Tablets

Sustained release tablets, each containing 500 mg metformin hydrochloride were prepared by wet granulation techniques. The composition of various formulations of the tablets with their codes is listed in Table 1. Calculated amount of the drug, polymer (Hydroxy propyl methyl cellulose) and filler (MCC) was mixed thoroughly. All the powders except magnesium stearate and talc were passed through 60 mesh sieve. Required quantities of drug and polymer were mixed thoroughly, and a sufficient volume of granulated agent of PVPK-30 solution was added slowly. After enough cohesiveness was obtained, the mass was sieved through 14 mesh sieve. The granules were dried at 50°C for 2 hrs in a hot air oven. Dry, the granules were passed through 20 mesh sieve. Talc and magnesium stearate were finally added as glidant and lubricant. Granules thus obtained were compressed using a an eight station rotary press (Rimek Minipress India) at a constant compression force equipped with a 14mm flat-faced punches at a compression force required to produce tablets of about 5-7 kg/cm2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Table 1 Composition of various trial formulations for the SR tablet containing 500mg metformin HCl.

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Metformin Hydrochloride	500	500	500	500	500	500	500	500
HPMC K-50	60	80	120	60	80	120	150	80
Microcrystalline cellulose	102	84	48	107	87	57	14	83
Maize Starch	10	10	10	10	10	10	10	10
P.V.P.K-30	18	16	12	13	13	13	16	17
Magnesium Stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight (mg)	700	700	700	700	700	700	700	700

2.3. Pre-compression parameter[5,6,7]

The granules were evaluated for angle of repose, loose bulk density; tapped bulk density, Compressibility index and Hausner's index etc. (Table 3)

2.4. Post Compression evaluation

The prepared tablets were characterized immediately for hardness, weight variation, friability and drug content[7]. The weight variation of the tablet was evaluated (n=10) tablets using an electronic balance. The tablet hardness (n=3)was tested by using Monsanto hardness tester. Tablet friability (n=10) was determined by using Roche friabilator for 4 minutes at a speed of 25 rpm. The thickness of the tablet determined using vernier caliper. Drug content (n=10) was determined by using UV/Visible spectrophotometer (Shimadzu 1800 Japan) by measuring the absorbance of standard and sample at 233nm for Table 4.

2.5. In-Vitro Drug Release Studies[8,9]

Release rate of all the designed formulations were studied up to 12 hours using USP- type lI dissolution apparatus at 50 rpm. 0.1N hydrochloric acid used as dissolution medium (900ml) for first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours, maintained at 37°C ± 0.5°C. Sample of 5 ml was withdrawn at specific time intervals throughout the dissolution study of 12 hours for analysis and replaced with fresh dissolution medium. After appropriate dilution the samples were analyzed at 233 nm. The release studies were conducted in triplicate.

2.6. Release Kinetics[7]

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order and Higuchi matrix model. Based on the r-value, the best-fit model was selected.

2.6.1. Zero order kinetics

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

$$_t = Q_o + K_o t \quad \text{----------(1)}$$

Where, $Q_{t=}$ amount of drug dissolved in time t,Q_o = initial amount of the drug in the solution and K_o = zero order release constant.

2.6.2. First order kinetics

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$\text{Log } Q_t = \log Q_o + K_1 t/2.303 \quad \text{----------(2)}$$

Where, Q_t = amount of drug released in time t,Q_o = initial amount of drug in the solution andK_1 = first order release constant.

2.6.3. Higuchi model (square root law)

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media and the equation is,

$$Q_t = K_H \cdot t^{1/2} \quad \text{----------(3)}$$

Where, Q_t= amount of drug released in time t,K_H = Higuchi dissolution constant.

3. RESULTS AND DISCUSSION

3.1. FTIR

FTIR studies revealed that metformin hydrochloride showed typical bands at 3240.52 and 3356 cm–1 due to N-H primary stretching vibration and a band at 2862.46 cm–1due to N-H primary stretching, and characteristics bands at 1651.12 cm–1 assigned to C=O stretching. No significant shifts of reduction in intensity of the FTIR bands of metformin hydrochloride were observed as shown in Fig. 1.

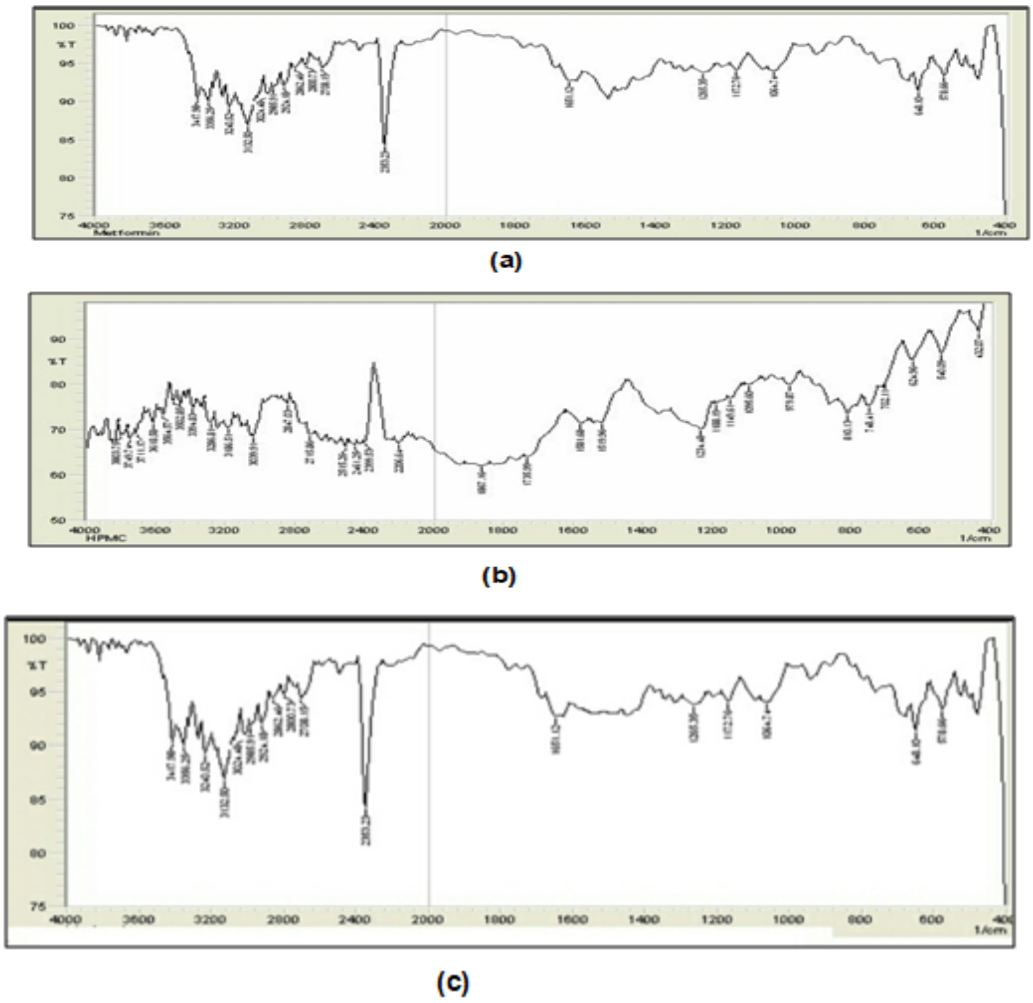


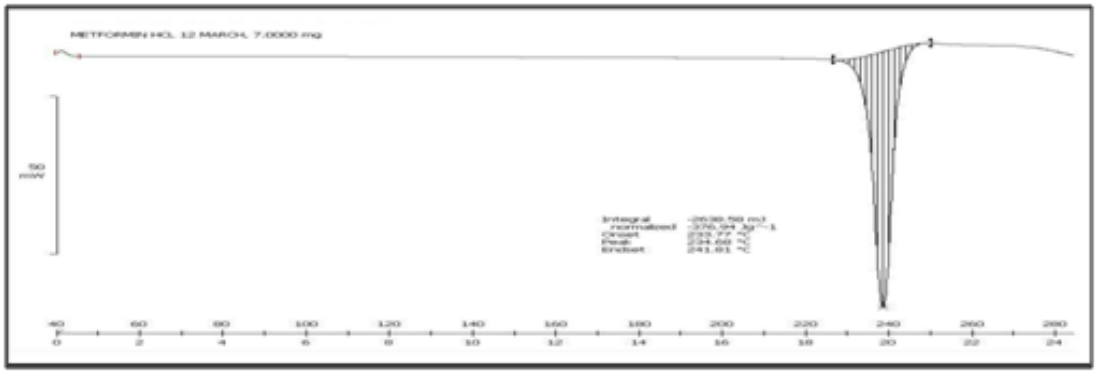
Fig. 1. (a) FTIR spectrum of Metformin Hydrochloride (b) FTIR spectrum of HPMC K-50 (c) FTIR spectrum F7 optimized batch formulation

Table 2 Observed IR Stretching.

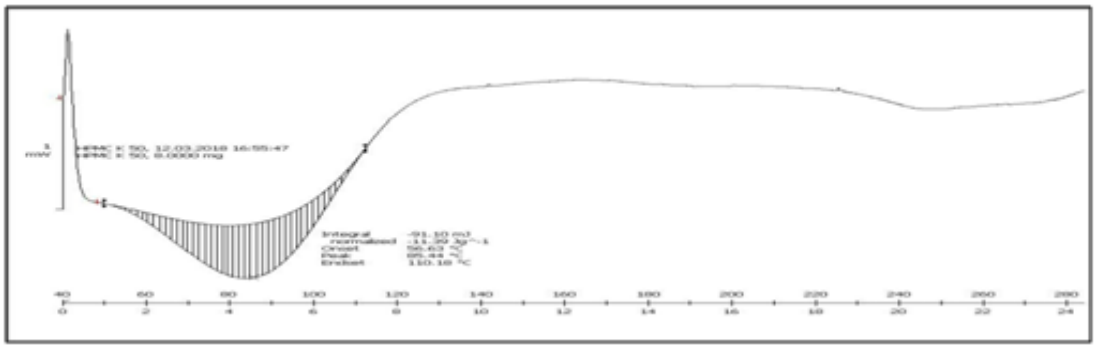
Frequency Cm-1	Wave number Found In Metformin	Groups Assigned
3200-3400	3240.52,3356.25,	-N-H-Stretching amine
2850 - 3000	2862.46,2924.18,2985.91	-C-H (stretching) Alkane
2700-2775	2708.15	-H-C=O stretching Aldehyde
1630-1680	1651.12	-C=O- stretching Amide

3.2. Differential scanning calorimeter (DSC) studies

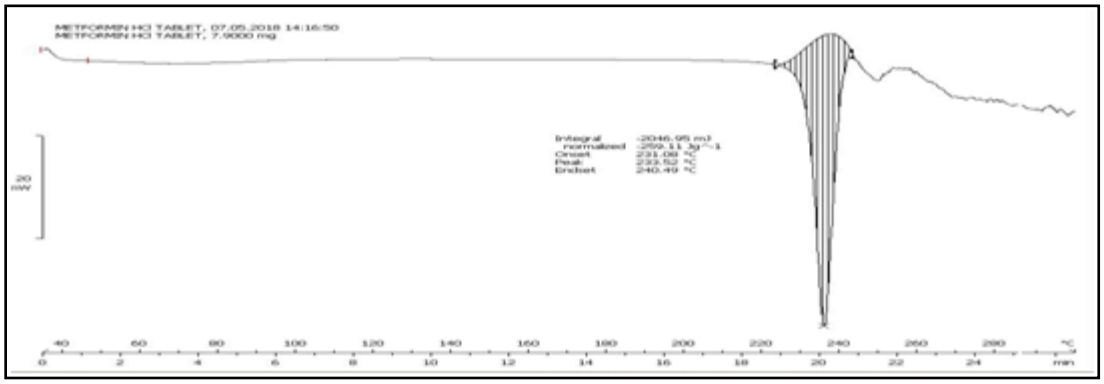
DSC analysis was performed in order to evaluate possible solid-state interactions between the components and consequently to assess the actual drug-excipient compatibility in all the examined formulations. The thermal curves of pure drug, components are shown in Fig. 2.



(a)



(b)



(c)

Figure 2 (a) DSC of Metformin HCl (b) DSC of HPMC K -50 (c) DSC Of F7 optimized batch formulation.

DSC curve of pure Metformin HCl exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the substance in the range 223–237°C (Tonset = 233.7°C, Tpeak = 234.68 and ΔH fusion = -376.94J/g). Superimposition of those of the single components, indicating the absence of solid-state interactions and allowing assessment of drug–

polymers compatibility in all the examined formulations. The tablet pre-compression and post - compression parameter for each formulation are presented in Table 3 and Table 4.

Table 3 Pre-compression parameter.

Formulation code	Bulk Density gm/ml	Tapped Density gm/ml	Hausner's Ratio	Angle of Repose [θ]	Compressibility Index %
F1	0.5633	0.5970	1.0598	30	5.64
F2	0.5797	0.6153	1.0614	23.07	5.78
F3	0.5882	0.6299	1.070	22.22	6.620
F4	0.5594	0.5830	1.0421	25	4.048
F5	0.5712	0.5988	1.048	23.07	4.60
F6	0.5594	0.6125	1.0949	21.42	8.669
F7	0.5540	0.6069	1.0954	20.68	8.71
F8	0.5583	0.5920	1.047	22.22	4.58

Table 4 Post -Compression parameter.

Formulation code	Hardness Kg/cm2	Thickness (mm)	Weight Variation (mg)	Friability % w/w	Drug Content %
F1	5.3	4.00	699.4	0.21	99.95
F2	5.36	4.02	699.5	0.13	100.35
F3	5.3	4.02	699.5	0.16	101.10
F4	5.2	4.02	699.3	0.15	100.12
F5	5.26	4.04	699.2	0.12	101.1
F6	5.36	4.02	699	0.14	99.08
F7	5.26	4.01	700	0.09	99.10
F8	5.33	4.01	700.1	0.23	100.99

3.3. In-vitro dissolution studies

All the eight formulations were subjected for the in vitro dissolution studies using tablet dissolution tester (USP) TDT-08L, Electro lab. The samples were withdrawn at different time intervals, filter, diluted and analyzed at 233 nm. Cumulative drug release (mg) and Cumulative % drug release were calculated on the basis of mean amount of Metformin Hydrochloride present in the respective tablet (Fig. 3). The drug released from formulation F1 to F3 containing HPMC K 50M at three concentration levels were found to be 68.70, 66.40 and 65.70 for Metformin Hydrochloride respectively. The drug released from formulation F4 to F6 containing HPMC K50 M at three concentration levels was found to be 84.90, 82.33 and 80.55 for Metformin Hydrochloride respectively. The drug released for formulation F7 containing HPMC

K 50 was found to be 92.80 for Metformin Hydrochloride respectively at the end of 12 hours. Best optimized batch was F7 because highest percentage drug release at the end of 12 hour among all the formulations

Table 5 In-vitro drug release profile of different formulations

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8
1	18.82	19.90	19.60	26.10	24.08	26.50	22.80	20.10
2	23.65	20.70	21.73	40.12	34.28	32.82	33.22	30.46
3	29.30	26.33	28.32	44.72	38.10	36.38	36.12	31.66
4	34.48	32.67	33.42	50.16	42.37	40.37	42.36	40.80
5	40.66	35.58	38.33	52.17	48.30	46.87	48.30	44.64
6	43.36	40.36	40.66	52.08	52.17	50.68	52.16	48.72
7	46.68	41.65	46.23	664.32	60.41	58.44	58.60	54.46
8	50.61	46.68	50.11	71.87	64.32	63.99	64.32	62.66
9	58.63	61.66	56.67	72.17	70.77	69.77	76.36	72.80
10	61.78	59.41	60.66	78.48	75.34	74.22	84.18	74.56
11	66.77	62.66	63.20	80.10	78.44	76.88	86.80	78.80
12	68.70	66.40	65.70	84.90	82.33	80.55	92.80	88.90

3.4. Effect of HPMC Viscosity

It is suggested that the hydrophilic polymer such as HPMC when comes in contact with the water, it absorbs water and swells to form an gel layer which serves as a barrier to drug diffusion. The drug release process from a HPMC matrix involves water penetration into the dry matrix, hydration and gelation of the polymer, dissolution of the drug and diffusion of the dissolved drug through the resultant gel layer. Since the movement of the drug through the matrix system is predominantly diffusion controlled, it may be expected from Stokes-Einstein equation, which states that the process will be slower in the more viscous layer regarding drug release profiles of the formulated tablets. It was observed that there was a gradual decrease in the rate of release of the drug from the polymer HPMC with increase in the viscosity.

3.5. In-Vitro Drug Release Kinetic

To describe the kinetics of drug release from tablets, release data was analyzed according to different kinetic equations. The data was analyzed by the regression coefficient method and regression coefficient value (r2) of all batches as shown in Table 6.

Table 6 Mathematical model of drug release

Formulation code	Zero order	First order	Higuchi
F1	0.974	0.0523	0.9753
F2	0.978	0.0632	0.9751

F3	0.984	0.0243	0.9575
F4	0.904	0.0283	0.9731
F5	0.945	0.0112	0.9658
F6	0.952	0.0028	0.9737
F7	0.969	0.0113	0.9637
F8	0.969	0.0280	0.9699

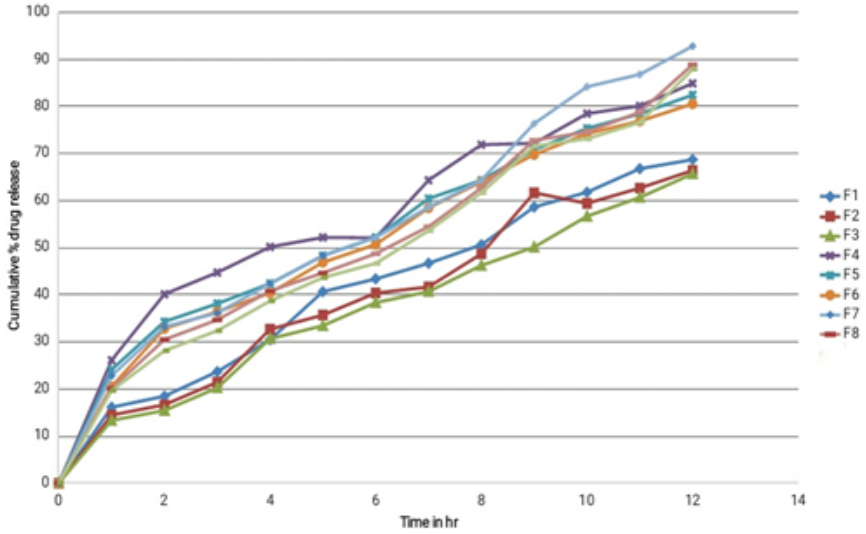


Figure 3 Comparative release profiles according to zero order kinetics.

4. CONCLUSION

From the present study carried out on Metformin hydrochloride sustained release tablet using HPMC K 50 M by wet granulation method, the following conclusion can be drawn. The results of current study clearly indicate that the in vitro release of Metformin is significantly affected by the amount & concentration of HPMC. As the concentration & viscosity of HPMC increases the drug release decreases significantly; polymers concentration & viscosity affects the drug release rate. All the formulation batches fulfill the official limit for physical parameters like weight variation, hardness, friability and drug content uniformity. The in-vitro drug release studies indicated that the optimum release profile was found by formulation batch F7. drug excipient interaction studies, no significant interaction was found. The optimized formulation of batch F7 give the best in vitro release of 92.80% in 12 hr in simulated intestinal fluid. The release of drug followed matrix diffusion mechanism. Our objective to retain the dosage form for longer duration on alkaline media have fulfilled and it definitely give the sustain release action for its antidiabetic activity. Hence it can be concluded that the formulation (F7) is a stable and effective for sustained drug delivery.

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