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Formulation and invitro evaluation of gastro retentive floating mini tablets of Metaprolol succinate and Hydrochlorothiazide

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ABSTRACT

Aim

The aim of the study is to develop and evaluate gastro retentive float tablets of metaprolol succinate and hydrochlorothiazide by using ethyl cellulose, carbopol971p, Hydroxy propyl methyl cellulose K15 M.

Materials and Methods

The bilayer tablets of metaprolol succinate and hydrochlorothiazide were prepared by direct compression method by using ethyl cellulose, carbopol 971P, Hydroxy propyl methyl cellulose K15 M in 10, 15, 20 % of each polymer.

Results

FTIR studies of the formulations showed no interaction of Metaprolol succinate and hydrochlorothiazide with the polymers used in formulation. Most of the tablet formulations showed values within the official limits for, pre and post-compression evaluation tests. The optimized formulation F9 with HPMC K15M and sodium bicarbonate showed best results based on required floating lag time of 102sec, floating duration release of 98.5% up to 16hrs.Formulaton F9 showed good results than rest of the 15 formulations in pre and post compression studies. IR-spectroscopic studies indicated that there were no drug-excipients interactions. The optimized formulation is F9 with 99.6 % in 12 hours. Drug release kinetics studies were done for F9 formulation; it followed zero order and Higuchi model release systems. The drug release from the formulation was sustained and followed non-fickian transport.

Conclusion

It is concluded bilayer technology has been successfully applied for sustained release of metaprolol succinate and immediate release of hydrochlorothiazide.

Keywords

Ethyl cellulose, Carbopol 971P, Hydroxy propyl methyl cellulose K15 M, Zero order, Non-fickian transport.

INTRODUCTION

Grater therapeutic effect of the drug substance can be achieved by prolonging the gastric retention of a dosage form. This is more applicable to the Drugs those are absorbed in stomach region[1]And the drugs that are less soluble or are degraded by the alkaline pH benefit from the gastric retention.[2,3]In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat Certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability,

therapeutic efficacy and possible reduction of the dose size[4,5].

MATERIALS AND METHODS

Metaprolol succinate and hydrochlorothiazide were gift samples from Pharma train Ltd, Hyderabad, India. Carbopol 971P, ethyl celluose, HPMC 15 M, Crosscarmellose sodium, Aerosil, Magnesium Stearate, Talc, Potassium Di hydrogen Orthophosphate, hydrochloric acid, were purchased from S. D. Fine Chemicals, Mumbai, India. All other ingredients used were of analytical grade.

FTIR STUDIES

The FT-IR spectrum of the obtained drug sample was compared with the standard FT-IR spectra of the pure drug. The knowledge of drug excipients interaction is useful for the formulation to select appropriate excipients. The overlain spectra of the two drugs were found to be appropriate after the estimation. Based on the point of maximum absorbance, the λ_{max} of Metaprolol succinate and Hydrochlorothiazide were found to be 222nm and 225nm respectively. The response for Metaprolol succinate was found to be linear in the concentration range of 10-30µgm/ml at 222nm with correlation coefficient of 0.994 in $6.8P^{H}$ buffer. The response for Hydrochlorothiazide was found to be linear in the concentration range of 2-6µgm/ml at 225nm with correlation coefficient of 0.997 in 0.1N HCl

Pre compression evaluation of mini tablets

Trial batches of different formulations of mini tablets were prepared and evaluated for the Angle of repose, Bulk density, Tapped density, Compressibility Index, Hauser's Ratio.

Preparation of mini tablets using polymers

In the present investigation, direct compression technique was employed to prepare tablets by using HPMC 15M, carbopol 971 P, ethyl cellulose at different drug to polymer ratios as per the composition given in Tables 1. Weighed quantities of ingredients were shifted through #30 mesh and mixed for 10mints in a polybag. Hydrochlorothiazide immediate release minitablets were prepared by direct compression technique, employing microcrystalline cellulose, croscarmellose sodium, Aerosil and magnesium stearate.

Table 1: Composition of extended release layer

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metaprolol Succinate	50	50	50	50	50	50	50	50	50
Ethyl cellulose	15	22.5	30	-	-	-	-	-	-
Carbopol 971P	-	-	-	15	22.5	30	-	-	-
HPMC K15 M	-	-	-	-	-	-	15	22.5	30
MCC	50	42.5	35	50	42.5	50	50	42.5	35
Mg. stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Sodium bicarbonate	30	30	30	30	30	30	30	30	30
Total weight	150	150	150	150	150	150	150	150	150

Composition of immediate release layer

Table 2: Composition of immediate release layer

Hydrochlorothiazide	12.5	12.5	12.5
Crosspovidone	5	10	15
MCC	80.5	75.5	70.5
Mg. stearate	1	1	1
Talc	1	1	1
Tablet weight	100	100	100

In vitro buoyancy studies

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) and duration of time the dosage form constantly remain on surface of medium is called the total floating time (TFT).The tablets were placed in a 250 ml beaker containing 100 ml of 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

In vitro dissolution studies

The release of from the prepared floating tablets was studied using USP-Type II paddle apparatus (Electrolab TDT 08L, dissolution tester, U.S.P.). Drug release profile was carried out in 900 ml of 0.1N HCl maintained at 37±0.5°C temperature at 100 rpm. 5 ml of samples were withdrawn at regular time intervals up to 12 h. The samples were replaced by equivalent volume of dissolution medium and were filtered through 0.45 µm what man filter paper. The samples were suitably diluted and analyzed at 279nm, using (Shimadzu UV 1700) UV spectrophotometer. To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi and Koresmeyer- Peppas equations. Based on the obtained R2values, the best-fit model was selected [16-18].Anomalous diffusion or non-fickian diffusion refers to a combination of both diffusion and erosion controlled rate release. The Korsmeyer Peppa's equation is used to determine whether the drug release mechanism is Fickian or non-Fickian.

IR Spectroscopy

The IR spectrum of Metaprolol Succinate pure drug was found to be similar to the standard spectrum of Metaprolol Succinate as in IP .The spectrum of Metaprolol succinate showed the following functional groups at their frequencies.

Compatibility Studies

This work exemplifies a general method of studying the drug excipient interactions, with the aim of predicting rapidly and inexpensively the long term stability of their mixtures. We study the physic-chemical properties of a drug (Metaprolol Succinate) in the solid state and in different combinations with several excipients (HPMC, Ethyl Cellulose). We compare the properties of pure compounds (untreated, or moisture/temperature conditioned) with those of binary mixtures drug: excipient which underwent the same treatment.

RESULTS AND DISCUSSION

Drug-polymer compatibility studies

The development of a successful formulation depends only on a suitable selection of excipients. Hence the physical states of metaprolol succinate and hydrochlorothiazide and the polymers (HPMC 15kM) individually and the combination of drug and polymers used for the preparation of formulations were studied by FTIR spectroscopy to know the drug-polymer compatibility.

Pre-compression flow properties of powder blend

The drug and polymer powders blends of different combinations were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose using standard procedures[13] and consistency in data obtained as indicated by their standard deviation values.

Bulk Density

Bulk density and tapped densities showed good packing ability of the powdered blend for compression process. Bulk and tapped densities of different formulations were calculated. The results of bulk density ranged from0.40±0.01to 0.39±0.018 and tapped density from0.48±0.005 to 0.48±0.005. Carr's index (Compressibility index): Carr's index of the powder of all formulations. Formulation F8 showed lowest Carr's index indicating good and passable compressibility.

Haunsner's ratio

Hausner's ratio ranged between1.14and 1.20. The powder blend of formulation LS5 showed lowest Hausner's ratio indicating good flow. Blend of LS8 had an excellent angle of flow as compared to those of other formulations

Angle of repose

The values were found in the range 11.29±13.0 to 32.73±2.0. The F5 had the lowest value among all formulations composition showing excellent flow. As per pharmacopoeia standards ranged in (25-30)

Preformulation values for sustained release layer (Metaprolol succinate)

Table 3: Pre Compression studies

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (°)
F1	0.40±0.01	0.48±0.005	16±1.48	1.2±0.04	32.73±2.0
F2	0.41±0.03	0.50±0.008	13.0±0.63	1.5±0.16	11.29±13.0
F3	0.50±0.5	0.58±0.06	13±0.63	1.16±0.07	31.58±1.2
F4	0.39±0.01	0.47±0.01	17.0±2.18	1.56±0.21	32.23±1.7
F5	0.37±0.03	0.41±0.05	9.75±2.93	1.1±0.11	32.35±1.8
F6	0.43±0.009	0.52±0.02	17.3±2.4	1.41±0.10	31.62±1.3
F7	0.44±0.016	0.50±0.008	12±1.3	1.1±0.11	29.92±0.1
F8	0.41±0.004	0.45±0.02	8.8±3.6	1.0±0.18	31.85±1.4
F9	0.39±0.018	0.48±0.005	18±2.8	1.23±0.02	31.96±1.5

Table 4: Post compression studies

Formu lation Code	% weight variation mg	Thickness± SD n=3 (mm)	%*friability	%Drug Content± SD n=3	Hardness (Kg/cm^2) ± SD n=3
F1	50	1.9±0.11	0.142	101.3 ±0.7	4.56 ±0.1
F2	50	1.8±0.11	0.151	102.3 ±1.4	5.03 ±0.4

F3	50	1.83±0.009	0.62	100.1 ±0.1	5 ±0.4
F4	50	2.1±0.03	0.154	100.7 ±0.2	4.63 ±0.1
F5	50	2.03±0.009	0.132	99.6±0.5	4.63 ±0.1
F6	50	2.3±0.009	0.143	98.9 ±0.9	4.2 ±0.11
F7	50	2.3±0.08	0.110	100.2± 0.07	4.7 ±0.24

Formulation Code	**% weight vaiation**	**Thickness± SD n=3 (mm)**	**%*friability**	**%Drug Content± SD n=3**	**Hardness (Kg/cm^2) hardness ± SD n=3**
F1	50	3.03±0.15	0.143	99.9 ±2.3	3.2 ±0.05
F2	50	3.9±0.18	0.123	101.2± 1.6	3.72 ±0.15
F3	50	3.10±0.12	0.106	100.3 ±1.4	3.13 ±0.12
F8	50	2.1±0.03	0.133	100.5± 0.1	4.53 ±0.12
F9	50	2.2±0.01	0.13	99.2±0.7	4.69 ±0.23

Hydrochlorothiazide immediate release tablets blend

Table 5: Pre compression studies

Table 6: Post compression studies

Formulation Code	**Bulk density (Kg/cm^3)**	**Tapped density (Kg/cm^3)**	**Cars index**	**Hausners ratio**	**Angle of repose (°)**
F1	0.37±0.01	0.41±0.02	9.75±1.2	1.1±0.04	26.14±2.4
F2	0.43±0.03	0.52±0.05	17.3±4.0	1.41±0.16	31.62±1.4
F3	0.36±0.01	0.39±0.03	7.6±2.7	1.0±0.12	31.03±1.0

Formulation of a mini matrix tablet

The bilayer tablet was prepared by wet granulation method. Development of bilayer tablets of Metaprolol succinate and Hydrochlorothiazide was carried out in three stages. Two layers (Immediate release layer and extended release layer) were formulated separately using different concentrations of polymers in different ratios. After optimization of individual layers by in vitro studies and statistical methods, bilayer tablets were prepared using optimized formula. Bilayer tablet was prepared using a rotary tablet compression machine. First, the extended release layer was precompressed on a compression machine and the immediate release layer was loaded on top of the precompressed layer and was compressed. Compositions of immediate and extended release layers are shown in the table.

Post-compression evaluation of metaprolol succinate floating tablets

The formulated floating tablets were subjected for post compressional evaluation such as visual inspection, hardness, weight variation, friability, uniformity of drug content, in vitro buoyancy, swelling, in vitro dissolution, stability and similarity studies. The results are summarized in Table 2

Hardness and friability

To test the hardness of the tablet Monsanto tester, Strong-cobb tester, the Pfizer tester, the Eureka tester, the Schleuniger testers are used. Friability is the tested for a tablet to see whether the tablet is stable to abrasion or not, it is tested by using Roche friabilator. This is made up of a plastic drum fixed with a machine which rotated at 25 rpm for 100 revolutions.

Weight variation

As per USP twenty tablets are weighed individually and an compendia weight is taken, the average weight is obtained by dividing the compendia weight by 20, now the average weight is compared to the individual weight of the tablet.

Compatibility Studies

This work exemplifies a general method of studying the drug excipient interactions, with the aim of predicting rapidly and inexpensively the long term stability of their mixtures. We study the physic-chemical properties of a drug (Metaprolol Succinate) in the solid state and in different combinations with several excipients (HPMC15M, sodium bicarbonate). We compare the properties of pure compounds (untreated, or moisture/temperature conditioned) with those of binary mixtures drug: excipient which underwent the same treatment.

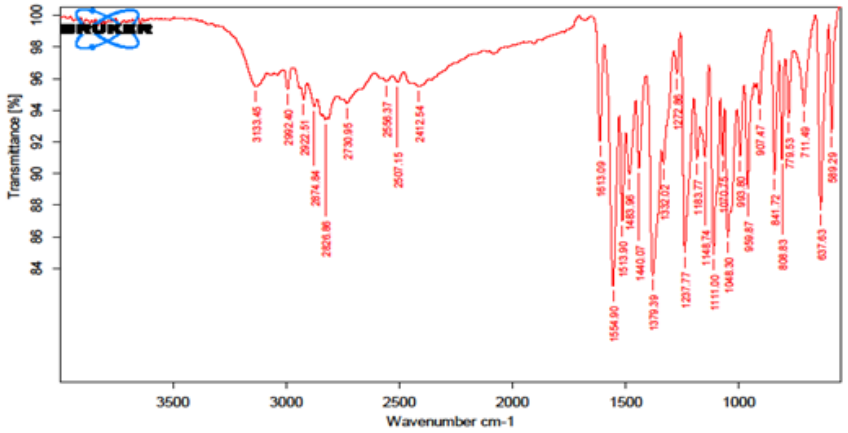

Figure 1: IR Spectra of Metaprolol succinate

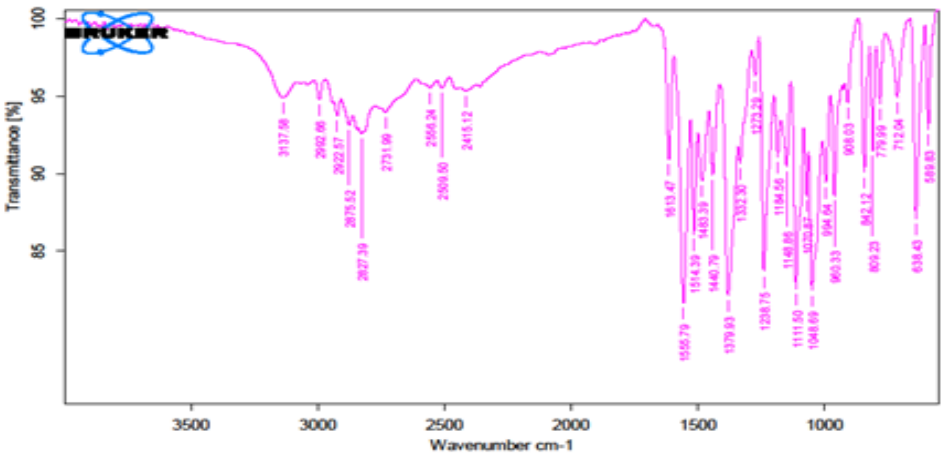

Figure 2: IR Spectra of Metaprolol succinate and HPMCK4M

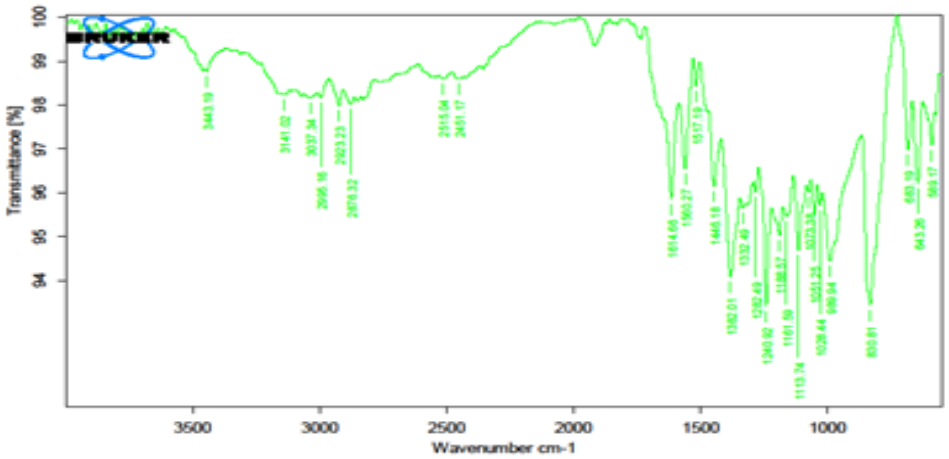

Figure 3: IR Spectra of Metaprolol succinate and Sodium bicarbonate

Table 7: Dissolution Data (Metaprolol Succinate)

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	16	15	20	17	14	11	21	18	15
4	75	69	63	58	53	49	63	58	51
8	99	94	89	81	84	80	91	89	85
10	100	100	96	89	93	85	98	96	94
12	100	100	100	98	98.4	94.6	99.2	99.1	99.6

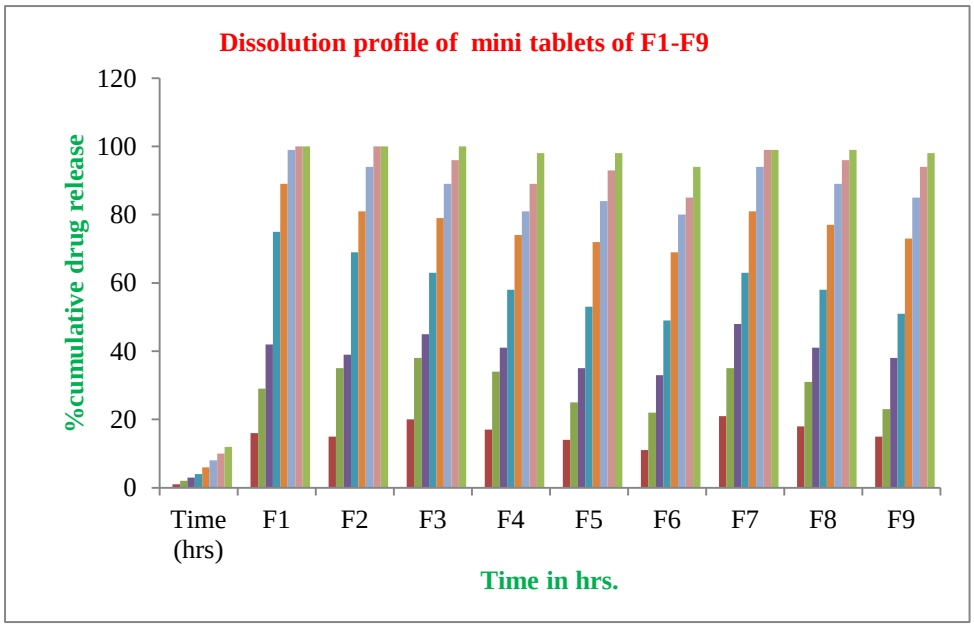

Figure 4: Dissolution profile of mini tablets of F1-F9

Table 8: Dissolution data for Hydrochlorothiazide immediate layer

Time (in min)	F1	F2	F3
15	64	69	81
30	89	92	100

45	96	97	100
60	98	99	100

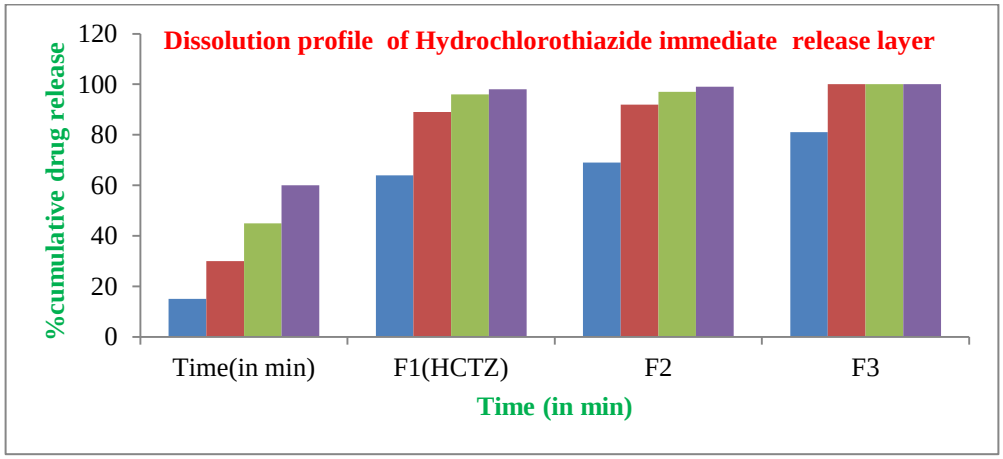

Figure 5: Dissolution profile of immediate release tablets

Table 9: Korsmeyer peppas equation log Time verses log % Drug Release (F7, F8, F9)

Time(hrs)	F7	F8	F9
0	0	0	0
1	21	18	15
2	35	31	23
3	48	41	38
4	63	58	51
6	81	77	73
8	94	89	85
10	99	96	94

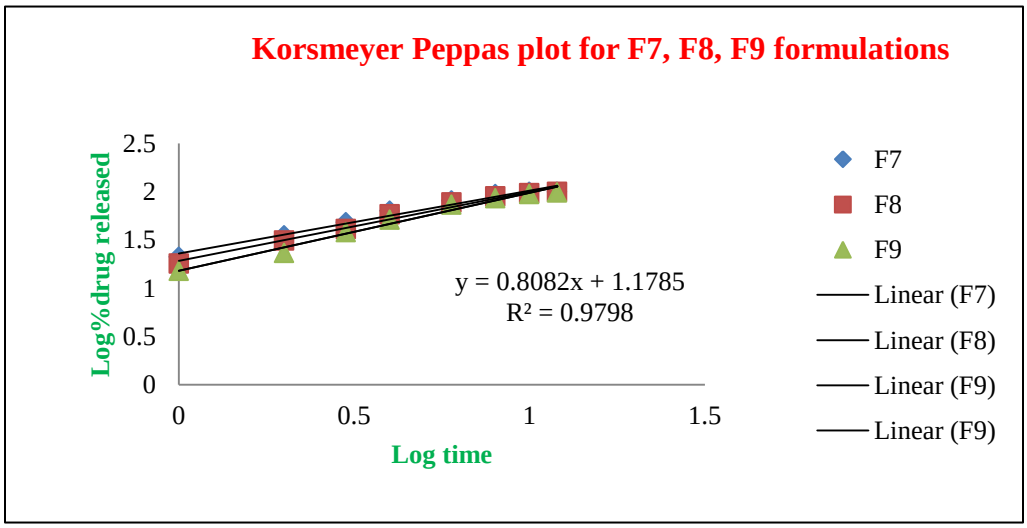

Figure 6: Higuchi plot -√Time verses % Drug release

CONCLUSION

The present research work was aimed to develop gastroretentive minitablets of metaprolol Succinate as extended release minitablets, hydrochlorothiazide as immediate release minitablets. Drug release from the matrix was found to decrease with increase in polymer concentration. Tablet formulations F1-F9 complied with the specifications for weight variation, thickness, hardness, friability, drug content and in vitro drug release. The optimized formulation is F9

with 20 % of HPMC K 15 M released 99.6 % in 12 hours. Drug release kinetics studies were done for F9 formulation; it followed zero order and Higuchi model release systems. The drug release from the formulation was sustained and followed non-fickian transport.

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