CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Original Article

A Mucoadhesive Bilayer Tablets for the Management of Type-II Diabetes Mellitus

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ARTICLE INFO

Received: 17 Mar 2016
Accepted: 15 Apr 2016

ABSTRACT

Over the past 38 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of novel drug delivery, greater attention has been focused on development of a modified release drug delivery systems. A mucoadhesive controlled release device can improve the effectiveness of drug by helping to maintain a drug concentration between the effective and toxic level, inhibiting the dilution of drug in the body fluid and allowing targeting and localizing of a drug at a specific site. The objective of the present study is to formulate the mucoadhesive Bilayer tablets of Metformin Hydrochloride and Glyburide .The mucoadhesive sustained release layer was formulated with Metformin Hydhochoide, along with Na-CMC and HPMC in combination as mucoadhesive polymers with ethyl cellulose as insoluble polymer to maintain the integrity of tablets. The immediate release layer was formulated with Sodium Starch Glycolate as super disintegrants. The bilayer tablets were formulated using wet granulation technique for mucoadhesive layer and direct compression for immediate release layer. All the physicochemical properties of the tablets were evaluated. The *exvivo* technique use to study the mucoadhesive strength and duration of the tablets against bovine intestine. From the study it found that the Formulation F2 with Na-CMC: HPMC in ratio 4:1 in mucoadhesive layer shows release of 89.17% of Metformin Hydrochloride in 12 hrs and 4% Sodium starch glycolate shows maximum release of 98.07% of Glyburide in first 10 minutes. The drug release follows the Higuchi release model and n value showed anomalous release profile. The swelling index increases with increase in the concentration of anionic polymers and its combination with non-ionic polymers. Increase in the swelling index leads to increase in mucoadhesion of the tablets. The mucoadhesion strength was found to be maximum for F2 formulation (0.287 N) and the tablet adhere to the membrane for more than 10 hrs. Effective mucoadhesive bilayer tablets were formulated using HPMC, Na CMC to deliver the drug for more than 10 hrs at the targeted site.

Keywords: Mucoadhesion, bilayer, *Ex vivo*, kinetics

1. INTRODUCTION

Over the past 38 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of novel drug delivery, greater attention has been focused on development of a modified release drug delivery systems. This factor

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such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. A mucoadhesive controlled release device can improve the effectiveness of drug by helping to maintain a drug concentration between the effective and toxic level, inhibiting the dilution of drug in the body fluid and allowing targeting and localizing of a drug at a specific site [1].

A drug can be incorporated in to a cross linked polymeric device that would adhere to mucous substrate in the body. [2]

The mucoadhesive bilayer is prepared with one layer of drug for immediate release with second layer design to release drug later as in sustained manner with mucoadhesive in nature.

The mucoadhesion process involves two steps. In the first step, intimate contact between a mucoadhesive material and a membrane is achieved. In gastrointestinal system, it is not possible to place the device; in such system the force promoting the adsorption is sufficient to hold them on mucosal surface. In the second step consolidation takes place by penetration of the mucoadhesive into the crevices of the tissue surface or inters penetration of the chains of the mucoadhesive with those of the mucus take place. For mucoadhesion to occur, the attractive interaction should be larger than non-specific repulsion [2, 3].

Biguanides, in particular, metformin Hydrochloride, increase sensitivity to insulin in peripheral tissues of the hosts. Metformin hydrochloride specifically use for the management of Type-I (Non insulin dependent) diabetes mellitus, affecting elevated plasminogen activator (PAI) levels both in Hypertriglyceridemia and in non insulin dependent diabetes conditions. [5]

It is also involved in inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis and inhibition of fatty acid oxidation [6].

The drug has an absolute oral bioavailability of 40 to 60 % and gastro-intestinal absorption is apparently complete within 6 hrs. An inverse relationship is observed between the dose ingested and relative absorption with therapeutic doses (0.5 to 1.5 g), suggesting the involvement of active, saturable absorption process [7]. Metformin Hydrochloride has limited window of absorption and absorbed from upper part of intestine. By the mucoadhesion technique it is possible to target the drug at the site of absorption. Hence Metformin Hydrochloride formulated as mucoadhesive sustained release layer.

Plasma half-life of Metformin Hydrochloride is 1.5 - 4.9 hrs [8]. Suitable dosage regimens of the drug include unit doses of 500 mg two to three times daily and can even be built up to five times daily or 850 mg once or twice daily. Furthermore, Metformin Hydrochloride presents formulation challenges due to its inherently poor compressibility, high dose and high water solubility (> 300 mg/ml at 25 ºC). It belongs to class III of Biopharmaceutical Classification System (BCS) having high water solubility and low permeability [9]. For drugs that are highly water soluble, both hydrophilic and hydrophobic matrix systems are widely used in oral controlled release drug delivery to obtain a desirable drug release

Glyburide is a second generation sulphonyl urea capable of stimulating insulin release, poorly acting on insulin resistance while Metformin hydrochloride able to act on insulin resistance, but not able to stimulate insulin secretion. [10]

Rationale for combination of Glyburide with Metformin hydrochloride suggests the use of combined formulations of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin resistance condition. 5mg of Glyburide and 500mg of Metformin hydrochloride is suitable for the treatment of Type-II diabetes mellitus at any time of

the progression of the disease. 5mg of Glyburide is required to reduce the hyperglycemic effect and 500 mg of Metformin hydrochloride is required to sustain the normal glycemic level for the Type-II diabetic patient. [11]

The combination therapy of bigunides and sulfhonyl urea produce synergistic effect in combination. Hence to reduce the dosing frequency and to improve patient compliance at particular site of absorption the combination therapy is taken to get synergistic effect or additive effect and dose of single component can be reduced.

Therefore an object to produce a bilayer tablet with two different release profiles with Glyburide as immediate release layer and Metformin hydrochloride as a sustain release layer to provide a desired pharmacokinetic and therapeutic action for the management of the disease condition. [12]

2. MATERIAL AND METHODS

Metformin hydrochloride was gifted by Sun Pharmaceutical Industries Pvt Ltd, Glyburide was gifted by Dr. Reddy's Laboratories, Hyderabad. Hydroxylpropyl Methyl Cellulose was gifted by Colorcon, Microcystalline Cellulose (Sigma Chemicals), Sodium Carboxyl Methyl Cellulose, Magnesium stearate (S.D Pharmaceuticals). All other reagents and chemicals used were of analytical reagent grade.

Methods

Drug-excipient interaction studies

Preformulation studies are very important for the successful formulation of any dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers, diluents and lubricants used in tablet formulations. In the present study 1:1 ratio was used for preparation of physical mixtures and analyzed for compatibility studies.

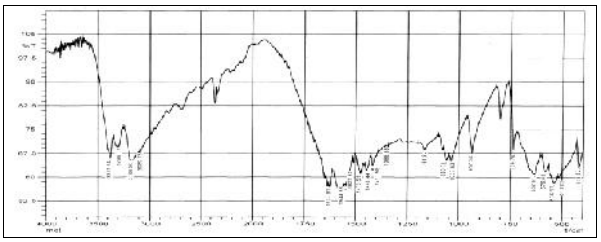

Fig 1: IR spectra of Metformin hydrochloride

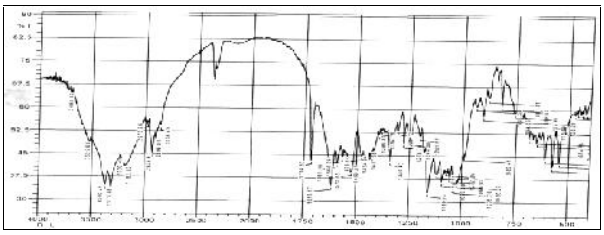

Fig 2: IR spectra of Glyburide

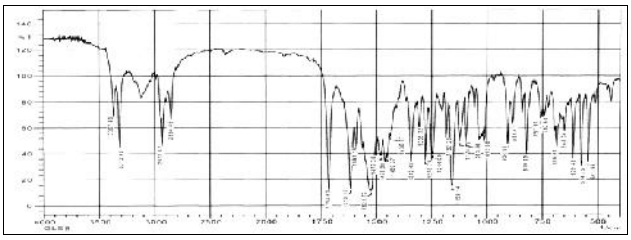

Fig 3: IR spectra of of Bilayer tablets

Preparation of Mucoadhesive Bilayer Tablets

Preparation of the Blend of Layer I With Metformin Hydrochloride

The mucoadhesive layer was fabricated using wet granulation technique. The ratio of the drug and the polymer used to prepared different batches is tabulated in table no 1.

Table 1: Composition of the Formulation of Mucoadhesive layer.

Formulation	Mucoadhesive Sustained release layer					Immediate release layer				Total
	Drug	NaCMC	HPMC	EC	Mg stearate	Drug	Lactose	SSG	Mg stearate	
F1	500	220	30	40	10	5	90	4	1	**900**
F2	500	200	50	40	10	5	90	4	1	**900**
F3	500	180	70	40	10	5	90	4	1	**900**
F4	500	160	90	40	10	5	90	4	1	**900**
F5	500	140	110	40	10	5	90	4	1	**900**
F6	500	110	140	40	10	5	90	4	1	**900**
F7	500	90	160	40	10	5	90	4	1	**900**
F8	500	70	180	40	10	5	90	4	1	**900**
F9	500	50	200	40	10	5	90	4	1	**900**
F10	500	30	220	40	10	5	90	4	1	**900**

All values are in mg. Na-CMC = Sodium carboxyl methyl cellulose, HPMC = Hydroxyl propyl methyl cellulose, EC = Ethyl cellulose, SSG = Sodium starch glycolate

The drug, Metformin hydrochloride along with Sodium carboxyl methyl cellulose (Na CMC), Hydroxyl propyl methyl cellulose (HPMC), Ethyl cellulose (EC) were blended together to form a uniform mixture of drug and polymers. A solution of alcohol and water (1:1) was prepared. This water alcohol solution was added to the drug polymer mixture to form the granules. This damp mass was forced manually to pass through the sieve no 16. Granules were dried at 60^0C for 4 hrs. Dried granules were passed through sieve no 22 to separate the granules from the fines. The resulting granules were mixed with Magnesium stearate for 5 min [4].

Preparation of the Blend of Layer II with Glyburide

The layer II was formulated by direct compression technique. The ratio of drug and polymers used is tabulated in table 2. The drug, lactose and disintegrants, Sodium Starch glycolate (SSG) and Crospovidone were blended together to form the uniform mixture. To this mixture Mg-stearate was added and blended properly. The immediate release layer was compressed alone to optimize the concentration of the disintegrant at the hardness of 1-2 kg [5].

Table 2: Composition of the Formulation of Immediate release layer

Formulation	Drug	Lactose	SSG	Crospovidone	Mg stearate	Total
GL1	5	92	2	-	1	**100**
GL2	5	90	4	-	1	**100**
GL3	5	86	8	-	1	**100**
GL4	5	92	-	2	1	**100**
GL5	5	90	-	4	1	**100**
GL6	5	86	-	8	1	**100**

All values are in mg. SSG-Sodium starch glycolate

Compression of Bilayer

The lubricated granules of MH layer I was fed to the die cavity as a first layer as the first layer was compressed very slightly to get uniform layer, then the optimized GL blend was added to the die cavity as the second layer and compressed finally to get bilayer tablets. A standard concave punch of 12 mm was used on cadmach single stroke compression machine for tableting [13].

Fig 4: Metformine Hydrocloride and Glyburide bilayer tablets

Evaluation of Mucoadhesive Bilayer Mtablets

All the prepared Bilayer tablets were evaluated for hardness, friability, disintegration test and Drug content. Weight variation was determined by weighing 20 tablets individually, the average mass was calculated and the percent variation of each tablet was calculated [14].

***In-Vitro* Dissolution Studies of the Tablets**

The dissolution medium for the bilayer tablets was modified. The dissolution was carried in two steps:

Step I: The release of Glyburide was carried out in 7.4 pH phosphate buffer with 8.5% of alcohol and 0.24% tween 80 as the drug is highly insoluble hence the dissolution media was modified as described by El-Massik. et.al. 2006 The temperature was maintained at 37^0C ± 0.5^0C in USP I apparatus in 900 ml. 10 ml of the sample was withdrawn, filtered and diluted suitably and analyzed by UV spectrometer at 227 nm [15]. The results are tabulated in table 3.

Step II: The release of Metformin Hydrochloride from mucoadhesive tablet was carried out in pH 6.8 phosphate buffer at 37^0 C ± 0.5^0 C in USP I apparatus. The basket was set at 100 rpm. 10 ml of the sample was withdrawn, filtered and diluted suitably and analyzed by UV spectrometer at 233 nm [16].

The release of drug from dosage form depends upon the type of polymer and other formulation parameter used. For finding the mechanism of drug release from combination of hydrophilic and hydrophobic polymer matrix tablets, the dissolution data obtained from the

above experiments was treated with the different release kinetic equations:

Higuchi square root of time equation:

$Q = K_H t^{1/2}$ …….. Equ1

Where Q is amount of drug release at time t, K_H is the Higuchi square root of time release rate constant [17].

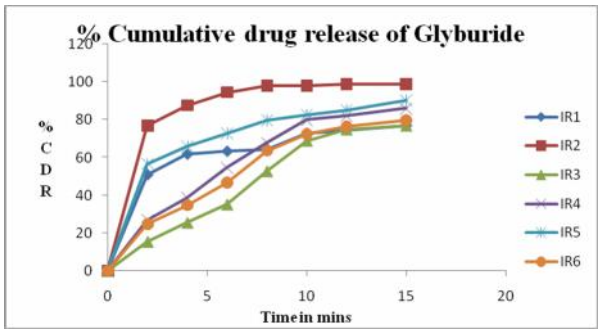

Fig. 5: % Cumulative drug release of Glyburide . (IR1-IR6)

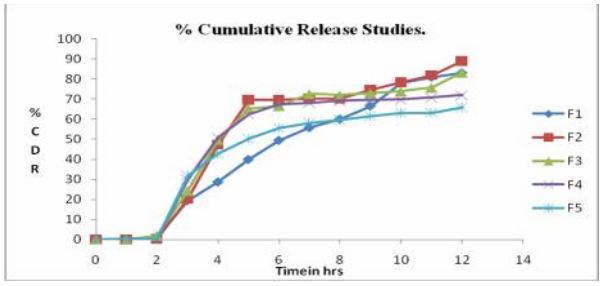

Fig 6: % Cumulative drug release of Metformin Hydrchloride (F1-F5)

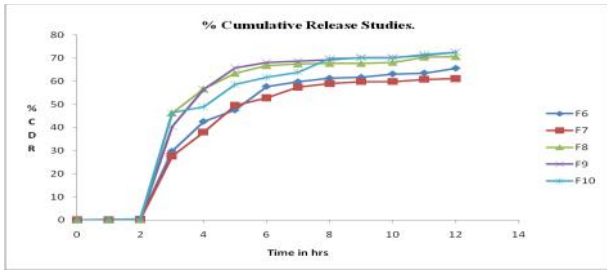

Fig 6: % Cumulative drug release of Metformin Hydrchloride (F1-F5)

Swelling Studies [18]

The extent of swelling was measured by taking different formulation of tablets and their initial weight was noted. Tablet from each batch was placed in Petri plate in pH 6.8 phosphate buffer. At time interval of 2, 4, 6, 8, 10, 12 hours tablets were removed from buffer medium and excess water on their surface was carefully absorbed with filter paper. The swollen tablets were weighed and swelling index was calculated.

$$\textbf{Swelling index} = \frac{W1 - W2}{W2} \times 100$$

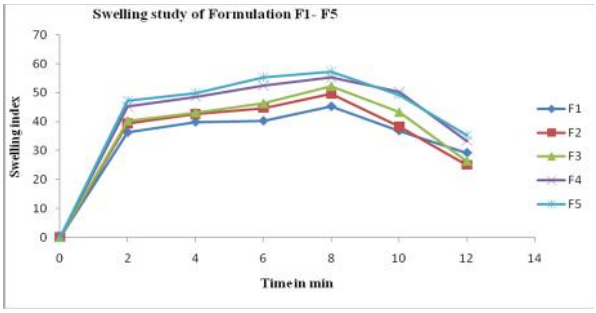

Fig 8: Swellings studies of Formulation F1-F5

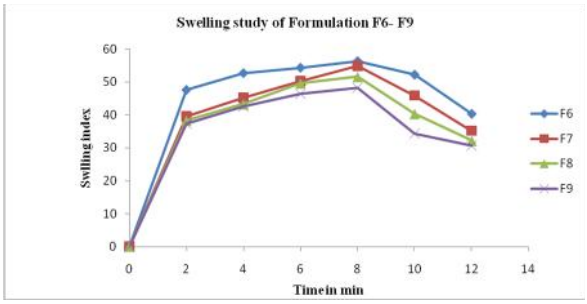

Fig 9: Swellings studies of Formulation F6-F9

Exvivo Mucoadhesive Studies

The tablet was studied for Force of mucoadhesion as well as duration of mucoadhesion.

Force of mucoadhesion using Bovine Intestine:

Bioadhesive strength of the tablet was determined by modified physical balance. The apparatus consist of a modified double beam physical balance in which right pan had been replaced by lighter pan and the left pan had been replaced by beaker. The left side of the balance was exactly 5 g heavier by right side. A teflon block was placed in a petri dish, which was placed below the left hand side of the balance.

Bovine Intestine was used for the study and phosphate buffer pH 6.8 was used as a moistening fluid. The mucosa was washed and spread on the Teflon block using thread. Peristaltic pump was used to pump the Phosphate buffer 6.8 at the flow rate 1ml/min.

Tablet was fixed to the lower side of the lighter pan and the tablet was made to adhere to the membrane. Water was added slowly with an increment of 0.5 ml till tablet just separate from the membrane [1, 3]. Results are complied in table no 3.

Duration of Mucoadhesion

Tablets were thereby attached to freshly excise intestinal bovine mucosa, which has been spanned on a stainless steel cylinder (Dissolution Apparatus USP I). The cylinder was placed in the dissolution apparatus according to USP containing phosphate buffer pH 6.8 at 37^0C. The fully immersed cylinder was agitated with 200 rpm. The detachment disintegration and erosion of the tablets were observed within a time period of 10 hrs [12]. The results are tabulated in table 3.

Stability Studies

The stability studies were carried out according to ICH and WHO guidelines to assess the drug and formulation stability QC1 [13]. Optimized formulation was sealed in aluminum packaging having a polyethylene coating on the inside. Samples were kept in a humidity chamber maintained at 45°C and 75% RH for 3 months. At the end of the study period, samples were analyzed for drug content, dissolution studies and detachment stress [13].

Table 3: Tablet Property of the formulation.

Formulation	Thickness (mm)	Hardness (kg)	% friability	Force of mucoadhesion (N)	Duration of mucoadhesion (hrs)
F1	5.20±0.2	6.5±0.5	0.475	0.277	>10
F2	5.18±0.2	6.4±0.4	0.632	0.287	>10
F3	5.21±0.3	6.4±0.3	0.198	0.276	>10
F4	5.19±0.1	6.5±0.6	0.523	0.281	8
F5	5.22±0.3	6.5±0.3	0.727	0.245	9
F6	5.17±0.5	6.6±0.6	0.618	0.250	8
F7	5.15±03	6.4±0.2	0.738	0.259	>10
F8	5.13±0.2	6.6±0.3	0.388	0.259	>10
F9	5.18±0.3	6.5±0.3	0.599	0.276	>10
F10	5.23±0.3	6.7±0.5	0.746	0.280	>10

Table 4: Kinetics treatment to optimized formulation (F2)

	R^2 value	Slope	Intercept
Higuchi's square root of time equation	0.9281	0.0284	1.8172

3. DISCUSSION

The tablets were formulated to overcome the disadvantages of the drug Metformin and to produce synergistic effect with Glyburide. Na.CMC is anionic and HPMC is non ionic polymers were selected as mucoadhesive polymer. EC is hydrophobic polymer is incorporated to retain the integrity of the dosage form as well as to target the drug to intestine [12].

In drug excipient interactions done by IR spectrophotometer, no interaction was observed in the IR spectra. All the principle peaks were observed in the bilayer spectrum.

As the drug Metformin is not free flowing, hence the wet granulation is selected in order to increases the size of the particles. And due to very small dose direct compression was selected for the Glyburide IR layer. The blends were evaluated for various properties and found to be satisfactory.

All the formulation showed uniform thickness, hardness, weight and drug content. Percent friability was found below 1% [7]. The results are tabulated in table no 3.

From *In-Vitro* release study, in initial 10 minutes, there was a complete release of drug Glyburide with 4% of Sodium Starch Glycolate with lactose, therefore it is considered as the optimized ratio for the IR layer. The dissolution profile was given in Fig 2.

Formulation F1, F2, F3 shows significant good release for 12 hrs with low burst effect. Among the three F2 shows maximum release. The drug release follows the Higuchi release pattern i.e. diffusion followed by erosion and n value shows anomalous release [10]. The dissolution profile is given in Fig 3 and 4.

The swelling behavior is important for bioadhesion. Water sorption increases with increase in the concentration of hydrophilic polymers [11]. In HPMC matrix the water uptake is low. The polymer swells slowly and dissolves in presence of water. Hence SI

with HPMC increases with time upto 8 hrs and then decreases. The reason behind this may be that as the time passes more the dissolution of outer gelled layer of tablets in dissolution medium [12].

In case of NaCMC is anionic polymer, the swelling increases with time but after certain period ingress of water get constant and decreases [11, 12]. Anionic polymer shows its minimum swelling in acidic condition, as the pH increases swelling increases.

In formulation F1 to F-7 the sharp increase in swelling which was due to combination of anionic polymer (NaCMC) and non-ionic polymer (HPMC) due to stronger hydrogen bonding between the carboxylic group and hydroxyl group leading to strong cross linking between the polymer. Further, F8-F10 there is decrease in swelling because of increase concentration of the low viscosity HPMC grade and decrease in concentration of anionic polymer [11, 14].

Mucoadhesion is determined by Mucoadhesive strength and duration of mucoadhesion.

Formulation F1-F4 shows good mucoadhesive strength. As the polymer viscosity increases swelling increases and mucoadhesion force depends on the swelling of the polymer. This improves the consolidation step that increases the mobility of molecule and facilitates the interpretation with mucus layer, thus mucoadhesion increases. F2 shows maximum mucoadhesive strength (0.287 N) [15, 16].

But further F5-F7 has least mucoadhesion strength; this is due to tremendous increase in viscosity, which leads to entangled structure of the polymer, which hinders the deep interpenetration between polymer and mucin molecules. But further F8-F10 the strength increases as there is decrease in viscosity [16, 17].

All the formulation except F5-F7 passes the test of mucoadhesion (Time = 12 hrs). The formulation F5-F7 fails to retain due to the over hydration of the formulation [18].

The targeting to the intestine can be achieved by the dynamic swelling behavior of crosslinked polymers which depend on the polymer relaxation at different pH. In anionic polymer networks, the polymer relaxation is significantly affected by the ionization of the functional groups of the polymer. An increase in the degree of ionization contributes to the electrostatic repulsion between adjacent ionized groups, leading to chain expansion, which, in turn, affects macromolecular chain relaxation. At lower pH, the ionization was not significant, and there were no interactions between ionized functional groups. Because of which polymer do not swell and hence passes to the intestine. In intestinal pH, networks swelled by a relaxation-controlled mechanism and leads to entanglement of polymers with mucin [1, 2]. Formulation was found to be stable for 3 months in accelerated condition.

4. CONCLUSION

From the present research it can be concluded that the mucoadhesive bilayer tablets of Metformin Hydrochloride and Glyburide improve the patient therapeutic efficacy by targeting it to the sight of absorption by using suitable combination of the polymers in suitable ratio and by the synergic effect of both the drug for the management of the diseases

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Conflict of Interest: None

Source of Funding: Nil