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FORMULATION AND EVALUATION OF INTERPOLYMER COMPLEXES OF CHITOSAN-SODIUM CARBOXYMETHYL XANTHAN GUM FOR COLON SPECIFIC DRUG DELIVERY OF BUDESONIDE

N. Ramya Krishna* [1], R.Sushmitha[2]

Department of Pharmaceutics, Marri Laxman Reddy College of Pharmacy, Dundigal, Hyderabad-500 043, Telangana, India.

ABSTRACT

The objective of the present study was to develop a colon targeted sustained drug delivery of budesonide for the treatment of Ulcerative Colitis (UC). Budesonide was a BCS class II drug with low solubility and high permeability. Budesonide is a potent corticosteroid with high topical anti inflammatory effect and little systemic effect. Tablets were prepared by wet granulation method using interpolymer complexes (IPC) as binder and coating agent. The IPC were prepared by using HPMC K15M and avicel pH102. The IPC were characterized by Fourier transform infrared spectroscopy (FTIR). The tablets coated with CH: SCMXG were evaluated for their micromeritic properties and quality control tests and were found to be within the acceptable limits. Formulation F12 was proved to be having good drug content, lag time and drug release in the colonic region when compared to other formulations. Stability studies were carried out for the optimized formulation F12 for a period of three months at 40^0C/75%RH. The results indicated that there was no change in physicochemical properties as well as in the *invitro* drug release even after the storage period of three months at 40^0C and 75%RH.

Keywords: Chitosan, controlled release, wet granulation, carboxymethyl xanthan gum, crosslinking, lag time.

INTRODUCTION

Inflammatory bowel disease (IBD) refers to two related but different diseases: ulcerative colitis (UC) and crohn's disease (CD). It is manifested in the form of localized inflammation of large intestine. The process of inflammation is facilitated by defects in both the barrier function of the intestinal epithelium of mucosal immune systems [1]. IBD is a lifelong disease with periods of active disease alternating with periods of disease control (remission). The treatment comprises of oral administration of non-steroidal anti-inflammatory agents, antibiotic, corticosteroids and immunomodulators. The primary objective of anti-IBD therapy is to reduce the colon inflammation. This requires frequent administration of anti-inflammatory drugs at high doses, which may lead to gastric ulceration, bleeding of other gastric complications [2]. Corticosteroids has been found to be effective in patients with active UC and CD, because of their broad and nonspecific anti-inflammatory effects, including inhibition of cytokinins, lymphocyte toxicity and reduction of arachidonic acid metabolites [3]. Budesonide was selected as model standard drug to treat IBD. Budesonide is a potent, synthetic non-halogenated corticosteroid with high topical anti-inflammatory effect and little systemic effects. It has low incidence of adverse effects and high topical effects and has important suggestions in the pharmacotherapy of IBD, both in treatment of UC and CD. It was found that less than 5% of drug was available beyond the ileum and cecum, and hence, colonic delivery still needs to be optimized by a more reliable targeted system. UC most often affects a continuous segment of colon ranging from a limited short segment to affecting the entire colon [4-6]. Colon specific drug delivery system is of importance when delay in absorption is desired from therapeutic point of view in treatment of diseases showing peak symptoms in early

Corresponding Author:- **N. Ramya Krishna** Email: ramyanara86@gmail.com

morning i.e. chronotherapy that are sensitive to circadian rhythms. As dosage forms remains longer in the colon rather than in the small intestine, hence colon specific formulations could be used to prolong drug delivery [7-8].

Delivery of the drugs to the colon via the oral route is valuable in treating diseases related to colon (Crohn's disease, ulcerative colitis, irritable bowel disease, carcinomas and infections) whereby high local concentration of drugs can be achieved at the site of inflammation. Colon targeting can be achieved by pH-dependent systems or pH independent systems. Drug release in pH dependent systems is easily influenced by nature of diet. Further, physiologically, a highly alkaline pH of 7.4 of the small intestine often contributes to premature drug release and failure of the pH-dependent release systems before reaching the colon [9]. The pH-independent release systems had a drawback of incomplete drug release and so should be combined with other polymers that are either soluble at colonic pH or capable of being degraded by colonic bacteria[10]. Treatment might be more effective if the drug substances were targeted directly to the colon. Lower doses might be adequate and if so systemic side effects may be reduced. The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. As colon is relatively free of peptidases such special delivery systems will have a fair chance for oral administration undigested, unchanged and fully active peptide drugs. The simplest method for targeting of drugs to the colon is to obtain slower release for longer period of time or immediate release in abundant quantity. The special placement of drugs into selected locations in the GIT is quite difficult due to physiological constraints, namely, motility and mucus turnover. In some cases drugs may be unstable in upper GIT and are generally not well absorbed from the lumen of the GIT due to their relatively large molecular size and high peptidase activity. Protecting drugs from hydrolysis in GIT and subsequently releasing these drugs in the ileum or colon may result in better systemic bioavailability. Specific systemic absorption in the colonic region offers interesting possibilities for the treatment of disease susceptible to circadian rhythms [11-14]. Many researchers have reported the use of natural or modified polysaccharides for sustained or colon delivery of drugs. However, these polysaccharides are required to be used in large quantities [15] for achieving colon drug delivery. This is probably due to high solubility of non-cross linked molecules in the acidic pH. Therefore, the recent emphasis is on the use of biodegradable polymer combinations that are cross linked with each other or with ions in order to make them insoluble in acidic pH. Chitosan-chondroitin sulphate interpolymer complexed film coated tablets have been reported for colon targeting [16]. Chitosan (CH) carries a net positive charge due to –NH3+ groups and can be easily cross-linked with other anions, oppositely charged drugs and polymers [17]. CH is easily degraded by lysozyme, by non specific cellulases and enzymes secreted by intestinal bacteria [18]. Xanthan gum has also been examined for use in colonic drug delivery [19]. However, natural gums being hydrophilic swell in the presence of dissolution media. Thus, there is a possibility of the entrapped drug leaking out prior to arrival of the dosage form at the site of absorption. Thus, there is a need to reduce the enormous swelling of the gums by cross linking.

Sodium carboxymethyl xanthan gum (SCMXG), a derivative of xanthan gum has been investigated for colon drug delivery. SCMXG microspheres were prepared by dropping a solution of SCMXG in a solution of divalent and trivalent metal ions. The Ba2+ cross-linked products were able to protect the drug under gastric pH conditions while Ca2+ ions cross-linked products were found to release the encapsulated drug when exposed to pH 7.4 i.e. intestinal pH [20].

MATERIALS AND METHODS

Materials

Budesonide was a gift sample from startech labs, Hyderabad (India). Xanthan gum (XG), Chitosan (CH), Avicel pH102, HPMC K15M, Magnesium stearate and Lactose was purchased from SD fine chemicals, Mumbai.

Method

Procedure for Sodium carboxymethylation of xanthan gum

Xanthan gum was derivatised to SCMXG having O-carboxymethyl substitution of 0.8 following the method reported previously [21]. Required amount of xanthan gum (2g) was dispersed in ice cold solution of 45% w/v sodium hydroxide. The dispersion was kept at 5-8°C with continuous stirring for 1h. Monochloroacetic acid solution (75% w/v) was added with stirring in the reaction mixture and the temperature was raised slowly to 15-18°C. After 30 min, the temperature was raised to 75°C and maintained for additional 30 min. The reaction mixture was, then cooled to room temperature, cut into small pieces and dried at 50°C. The dried product was milled, washed with 80% v/v methanol and again dried [21].

Preparation of CH-SCMXG interpolymer complexed films

Chitosan (300mg) was dissolved in 15ml of 3%v/v acetic acid solution. To this mixture 8ml of 5M ammonium acetate solution was added. Sodium carboxymethyl xanthan gum (300mg) was separately added to chitosan solution by dissolving in 7ml of distilled water with continuous stirring. This mixture was poured into petri plates and dried at 50^0C for 48hrs. Films containing 50:50 ratio of CH: SCMXG were prepared using this method. The dried films were stored in a dessicator until use.

Formulation Budesonide tablets

Preparation of sustained release budesonide tablets

Tablets (average weight 200mg) containing budesonide were prepared by wet granulation technique. Budesonide and Avicel® pH 102 were granulated using CH: SCMXG solution of 10% w/w as binder. The granules were passed through #16 and dried at 50 ± 2^0C to 2-3% w/w residual moisture content. The dried granules were passed through #20 sieve and fines were retained on #44 sieve. 10% w/w of fines was admixed with the granules. 1%w/w of magnesium stearate was added to the granules. Granules were evaluated for micromeritic properties such as bulk density, tapped density, compressibility index, hausner's ratio and angle of repose. Tablets were compressed using cadmach tablet compression machine. The formulations were given in table 1. These tablets were evaluated for hardness, friability and weight variation and drug content.

Coating of Budesonide tablets

The formulated budesonide tablets containing CH: SCMXG solution as binder was coated with aqueous solutions containing 50:50 ratio of CH: SCMXG to obtain a weight gain of 5%, 10% and 15%w/w. The polymer concentration was varied. The coating solution was sprayed at a rate of 5ml/min with the help of peristaltic pump using a spray nozzle in a coating pan from the centre to the periphery for easy controlling of tablets thereby ensuring efficient mass transfer of polymer. The coated tablets were also evaluated for weight variation and drug content.

Evaluation of granules

Bulk density

The bulk density was determined by dividing the mass of microspheres by the bulk volume. The sample (10g) introduced into a 100 ml graduated cylinder and measuring its volume and weight "as it is"[22]. It was calculated by using the following equation.

Bulk Density (g/ml) = Mass of the powder (gm) / volume occupied by the powder (ml)

Tapped density

The tapped density was determined by dividing sample by the tapped volume. The sample (10g) was carefully introduced into a 100 ml graduated measuring cylinder. The cylinder was dropped onto a hard wooden surface for 100 times from a height of 1 inch with 2 seconds time interval until a constant volume is obtained. The tapped density of each formulation was then obtained by dividing the weight of the sample in grams by the final volume in ml contained in the cylinder [22]. It was calculated by using the following equation.

Tapped Density (g/ml) = Mass of the powder (gm) / volume occupied by the powder (ml)

Hausner's ratio

It provides an indication of the degree densification which could result from vibration of the feed hopper. Hausner's ratio closer of less than 1.25 indicates good flow, while greater than 1.5 indicates poor flow [23]

Hausner's ratio = Tapped density / Bulk density

Compressibility Index or Carr's index

A simple test was used to evaluate the flow ability of a powder by comparing the poured density and the tapped density of a powder and the rate at which it is packed down. High density powders tend to possess free flowing properties. A useful empirical guide is given by the compressibility index calculated from bulk density and tapped density [23].

Carr's index = (Tapped density – Bulk density / Tapped density) x 100

Angle of repose

Granules flowability was determined by calculating angle of repose by funnel technique. About 10g of granules was slowly passed along the wall of funnel till the tip of the pile produced and touches the stem of the funnel. A rough circle was drawn about the pile base and the radius of the sample cone was measured [24]. Angle of repose was calculated from average radius using formula:

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

Where, θ = angle of repose, h = height of the pile, r = average radius of the powder cone

Evaluation of tablets

Tablet thickness

Tablet thickness were accurately measured by using digital vernier caliper in mm [25]

Hardness and friability

Hardness of the tablet was determined by Monsanto hardness tester. Friability test was done by Roche friabilator. Ten tablets were weighed and were subjected to the combined effect of attrition and shock by using a plastic chamber that revolve at 25 rpm dropping the tablets at a distance of 6 in. with each revolution. Operated for 100 revolutions, the tablets were dusted and reweighed [26]. The percentage friability was calculated.

$$F = (W1 - W2 / W1) \ 100$$

Where, F is the percentage weight loss and W1 and W2 are the initial and final weights respectively.

Weight variation

Twenty tablets were selected at random and average weight was determined. Then individual weights were compared with the average weight [26].

Drug content uniformity

5 tablets were taken and crushed into powder and then weigh accurate quantity of powder equivalent to 9mg

of budesonide were transferred to the conical flask and suitably diluted with 10ml of 7.4 pH phosphate buffer respectively. The solution was filtered through whatmann filter paper and assayed at 245nm, using a schimadzu UV spectrophotometer [27].

***In vitro* release kinetics of budesonide from coated tablets**

In vitro release of budesonide from the coated tablets was carried out using rotating basket method specified in the USP XXIII dissolution tester at a rotation speed of 50rpm in 900ml of dissolution medium at 37 ± 0.5^0 C in media with pH 1.2 for 2h, pH7.4 for 3h and pH 6.8 till the end of the test. 5ml aliquots of the dissolution fluid were removed at specified time intervals and replaced with fresh dissolution medium and assayed for the amount of budesonide by UV spectrophotometer at wavelength 245nm. The dissolution data was analyzed to calculate percent drug released at different time intervals [28-29].

The mechanism of drug release during *invitro* dissolution studies in the respective media was studied by using the korsmeyer peppas [30] equation

$$\mathbf{Mt / M\infty = Kt^n}$$

Where, 'Mt' is fraction release of drug,'t' is release time, 'K' is kinetic constant which structural and geometrical characteristics of the device. 'n' is the release exponent which indicates the kinetic release. A value of 0.45 indicates the diffusion controlled drug release (fickian release). Case II transport or relaxation is indicated by a value of 0.89. Values of 'n' between 0.45 and 0.89 are regarded as an indicator of non-Fickian release or anamolous transport. The non-Fickian release is a combination of diffusion and polymer relaxation. Supercase II transport is indicated when the values of 'n' are greater than 0.89.

Stability study

Stability study was carried out for formulations to assess its stability, as per ICH guidelines. The optimized formulation were wrapped in the aluminum foils and was placed in the accelerated stability chamber at elevated temperature and humidity conditions of 40^0C/75% RH and a control sample was placed at an ambient condition for a period of three months. Sampling was done at a predetermined time of initial 0, 1, 2 and 3 months interval respectively. At the end of the study, samples were analyzed for the drug content, in vitro drug release and other physicochemical parameters [31-32].

RESULT AND DISCUSSION

Granules evaluation

The physical characteristics of the granules (F1-F12) such as bulk density, tapped density, Carr's index, hausner's ratio and angle of repose were determined. The results are given in table 2. The bulk density and the tapped density values were ranged from 0.909-0.984 and 1.102-1.148 respectively. The carr's index values were ranged from 0.108-0.174. The hausner's ratios were found to be within the limit of 1.124-1.211. The angle of repose of all the formulations was found to be between the limit 23.28-26.24. All the formulations showed good flow properties. The results were given in table 2.

Tablet thickness

The thickness of the tablets range from 2.99 -3.05 mm respectively. There is no variation in tablet thickness between the formulations. The results are given in the table 3.

Hardness, friability and weight uniformity of tablets

Hardness of the tablet was within the range and optimum for controlled release, and ranging from 7.2-7.6Kg/cm^2. The friability of all formulations was found to be in the range of 0.093-0.224% w/w and passes as per IP limit should not be more than 1% w/w. The weight uniformity of tablet in all formulation was observed to be within the IP limit 10%. All the formulations were complying with the official test. The values were mentioned in table 3.

Drug content

The assay of all the formulations from F1-F12 was found to be between 97.31-99.56%. The result shows that all formulations contained the drug within the limit. The values were mentioned in table 3.

***In vitro* drug release study**

Drug release study was conducted in pH 1.2, 7.4 and 6.8 simulated to stomach, small intestine and colon respectively. The cumulative percent drug release for all the formulations were shown in Fig-1 and Fig-2. The release kinetics of budesonide from coated tablets containing CH-SCMXG solution as binder and coating agent was analyzed by Korsmeyer peppas model. The value of r^2 was found to be above 0.9 and the value of 'n', release exponent was found to be in the range of 0.44-0.60. This indicated that the drug release from budesonide formulations follows non-Fickian release or anamolous transport. The non-Fickian release is a combination of diffusion and polymer relaxation. So, it can be indicated that the interpolymer Complexation of chitosan and sodium carboxymethyl xanthan gum was resistant to different pH media and the release of drug occurred due to slow erosion of polymer.

The mechanism of drug release during dissolution studies in pH progression media or in the presence of chitosanase was evaluated by using the Korsmeyer equation [17].

$$\infty = \frac{Mt}{M} = Ktn$$

Where, Mt/M

∞= fractional release of drug, t = release time, k = kinetic constant, which incorporates structural and geometric characteristics of the device.
n = release exponent, which indicates the kinetic release.

A value of 0.45 for 'n' indicates the case of diffusion-controlled drug release (Fickian release). Case II transport or relaxation controlled delivery is indicated by a value of 0.89. Values of 'n' between 0.45 and 0.89 are regarded as an indicator for the non-Fickian release or anomalous transport. The non-Fickian kinetics is suggestive of a combination of diffusion and polymer relaxation. In addition, Super Case II kinetics is indicated when the values of 'n' are greater than 0.89

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Accelerated stability study

Budesonide optimized formulation F12 was found to be stable for drug content 98.64, 98.62, 98.50 and 98.26% at 0, 1, 2 and 3 months respectively at 40^0C/75% RH. In vitro drug release of optimized formulation was found to be 93.39, 92.15, 91.35 and 91.24% respectively at 0, 1, 2 and 3 months respectively at 40^0C/75% RH. Results obtained were found shown in table 5. Finally it was observed that there was no change in physicochemical as well as in drug release profile even after storage at 40^0C/75% RH for three months. It may be inferred that there was no degradation of physical properties of the formulation.

Table 1. Composition of Budesonide formulation

S.NO	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Budesonide	9	9	9	9	9	9	9	9	9	9	9	9
2	HPMC K15M	15	20	25	30	15	20	25	30	15	20	25	30
3	Avicel pH102	20	20	20	20	20	20	20	20	20	20	20	20
4	Lactose	146	141	136	131	146	141	136	131	146	141	136	131
5	Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10	10
6	CH:CMXG (as binder)	10	10	10	10	10	10	10	10	10	10	10	10
7	CH:CMXG (weight gain%)	5%	5%	5%	5%	10%	10%	10%	10%	15%	15%	15%	15%

Table 2. Evaluation of budesonide sustained release tablet formulations

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio	Angle of repose (degrees)
F1	0.966	1.138	0.151	1.178	23.28
F2	0.970	1.102	0.119	1.136	23.31
F3	0.909	1.101	0.174	1.211	25.18
F4	0.986	1.106	0.108	1.122	26.24
F5	0.949	1.128	0.158	1.188	24.18
F6	0.963	1.164	0.172	1.208	25.64
F7	0.976	1.154	0.154	1.182	23.70
F8	0.958	1.138	0.158	1.188	24.28
F9	0.973	1.126	0.136	1.157	26.19
F10	0.984	1.106	0.110	1.124	25.36
F11	0.975	1.148	0.151	1.177	24.43
F12	0.964	1.135	0.150	1.177	25.15

Table 3. Evaluation of budesonide sustained release tablet formulations

Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	3.01	7.6	0.186	208	99.21
F2	2.99	7.2	0.093	207	97.27
F3	3.05	7.5	0.098	212	99.36
F4	3.02	7.4	0.125	208	97.31
F5	3.01	7.6	0.105	218	98.46
F6	3.02	7.2	0.095	220	99.56
F7	3.04	7.5	0.142	219	97.39
F8	3.05	7.4	0.134	221	99.37
F9	3.01	7.5	0.224	229	98.62
F10	3.03	7.9	0.096	229	98.64
F11	3.04	7.3	0.116	233	99.19
F12	3.04	7.6	0.156	230	98.64

Table 4. Cumulative percent drug release of sustained release budesonide formulations

Media	Time (hr)	Cumulative % drug release											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
	0	0	0	0	0	0	0	0	0	0	0	0	0
pH 1.2	1	14.85	10.48	8.64	5.12	0	0	0	0	0	0	0	0
	2	29.12	28.62	26.36	23.64	9.24	0	0	0	0	0	0	0
pH 7.4	3	48.19	43.18	40.29	40.16	24.18	8.96	8.04	0	0	0	0	0
	4	66.24	59.64	54.36	53.28	38.26	24.34	23.86	6.24	0	0	0	0
	5	83.47	73.19	67.19	64.16	49.34	38.16	36.06	21.39	10.28	0	0	0
pH 6.8	6	93.84	85.68	77.64	73.09	58.79	51.24	48.24	34.17	25.64	9.24	7.56	5.24
	7	-	95.19	85.42	82.16	66.14	62.79	59.24	45.64	39.16	28.19	24.24	25.16
	8	-	-	92.54	90.78	73.28	71.26	68.68	55.28	52.08	44.68	43.78	44.28
	9	-	-	98.99	97.75	80.36	79.58	74.39	63.46	64.19	59.24	57.26	57.71
	10	-	-	-	-	87.54	86.04	80.36	71.35	75.25	72.18	70.39	73.68
	11	-	-	-	-	94.19	92.69	85.64	79.89	85.38	84.4	82.64	89.26
	12	-	-	-	-	-	-	89.28	87.46	94.46	92.26	89.86	93.39

Table 5. Results of accelerated stability study of optimized formulation F12

	Optimized formulation	
	Drug content (%)	**% drug release**
Initial	98.64	93.39
One month		
Ambient	98.54	92.36
40^0C / 75%RH	98.62	92.15
Two month		
Ambient	98.52	91.46
40^0C / 75%RH	98.50	91.35
Three month		
Ambient	98.35	91.64
40^0C / 75%RH	98.26	91.24

Fig 1. Cumulative percent drug release of budesonide sustained release tablet formulations (F1-F6)

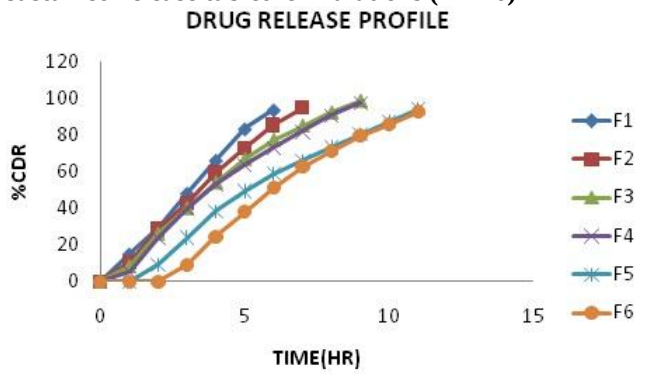
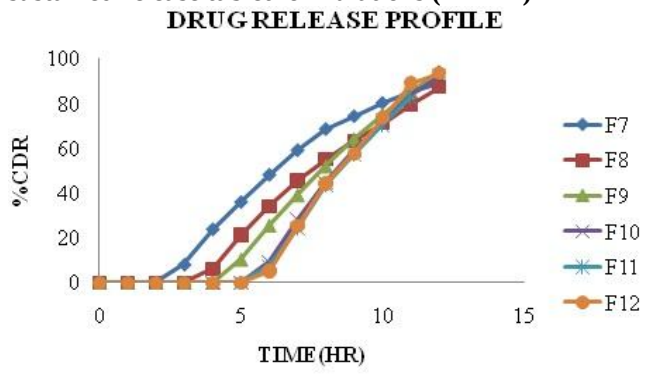


Fig 2. Cumulative percent drug release of budesonide sustained release tablet formulations (F7-F12)



CONCLUSION

UC and CD are two features of IBD. They are recognized by chronic relapsing inflammation in the whole GI tract from mouth to anus. Recently researchers have shown an increased interest in investigating the effect of different anti-inflammatory drugs used for the treatment of IBD. Hence budesonide a first line therapy drug for long term treatment of CD and for effective short term remedy to treat UC, was selected in this research work. In the formulation after budesonide mixed with HPMC K15M in order to produce sustained release and the outer functional CH: SCMXG coat. It was observed that the process parameters and solution composition (10%) used in CH: SCMXG coating to achieve different weight gain resulted good sustained release. Increasing level of HPMC K15M prolongs the drug release over outer CH: SCMXG coat which confirms that the formulation has ability to target drug release in the entire colon for the treatment of UC.

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CONFLICT OF INTEREST

None declared.

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