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FORMULATION AND EVALUATION OF GASTRORETENTIVE DRUG DELIVERY OF ORNIDAZOLE *INSITU* GELLING SYSTEM USING GELLAN GUM

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ABSTRACT

The aim of the present study is an attempt to formulate and evaluate gastroretentive drug delivery of Ornidazole insitu gelling system by using Gellan gum as a gelling polymer and calcium chloride as cross-linking agent for potentially treating gastric ulcer, associated with H.pylori. Gellan gum based Ornidazole floating in situ gelling systems were prepared by dissolving varying concentration (0.5-2.0%) of Gellan gum in combination of both use (0.25-1.0%) in deionized water. The formulation variable like concentration of Gellan gum significantly affected the in vitro drug release from the prepared formulations. The *in vitro* drug release studies were performed in0.1N Hcl at pH 1.2. Drug and physical mixture were characterized by FTIR, the result of IR study showed that no interaction between drug and polymers and other formulation parameters of formulated insitu gel are evaluated which showed better results. It was concluded that the formed gel showed prolonged gastrointestinal residence time and enhanced Ornidazole stability resulting from the floating insitu gel of Ornidazole. It might contribute better patient compliance while reduce frequency of dosing and by acceptable sustained-release dosage forms Ornidazole in the stomach to promote a fast and effective eradication of H.pylori to cure peptic ulcer. From the, viscosity analysis, *In vitro* buoyancy studies and release kinetics studies it can be concluded that the formulation FB1 has better potential of sustaining drug release with good gastric retention capability.

KEYWORDS

Oral insitu gelling system, Controlled delivery, Ornidazole, Floting drug delivery and Gellan gum.

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INTRODUCTION

Several approaches have been proposed to increase the gastric residence time of dosage forms such as buoyancy or floating system[1], floating in-situ gelling systems, hydro dynamically balanced system[2], expanding or swelling system, bio/mucoadhesive system[3], sedimentation or high density system, geometry or modified shape system may also use to increase gastric residence time.

In situ gel forming drug delivery is a type of mucoadhesive drug delivery system. Insitu gel forming drug delivery system is a revolution in oral drug delivery. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in PH. The insitu gels have a characteristic property of temperature dependant and action induced gelation[4]. These insitu gel preparations can be easily formulated in bulk, it gives site specific drug delivery and sustained action when compared to other conventional suspensions. The polymers which are used to prepare in situ gels can be termed as smart polymers. They are having the ability to change their physicochemical properties in response to the altered environmental conditions. The in situ gel formation occurs due to one or combination of different stimuli like PH change, temperature change, ionic activation etc. The insitu gelling system scan be applied in different routes like oral, nasal, ophthalmic, inject able, and vaginal route. Various natural and synthetic polymers can be used in the preparation of insitu gels like alginates, gellangum, xyloglucan, pectin, chitosan, PLA and carbopol. The insitu gel forming polymeric formulations are having several advantages like sustained and prolonged action compared to conventional drug delivery system, ease of administration, deliverance of accurate dose as well as to prolong residence time of drug, reduced frequency of administration, improved patient compliance and comfort. This system is also suitable from the manufacturing point of view as the productions of them are less complex and lowers investment and manufacturing cost[5]. Helicobacter pylori (H. pylori) are reported to be an important etiologic factor in the development of the gastritis, gastric ulcer and carcinoma in human stomach. H. pylori reside mainly in the gastric mucosa layer and epithelial cells of the antral region of the stomach. There are two major reasons for the failure of H.pylori eradication with convention a dosage forms of antimicrobials. One reason may be the degradation of antimicrobial agents by gastric acid, the before, the administration of high doses of antimicrobial agents on a daily basis is necessary for H.pylori eradication, but they are usually accompanied by adverse effects and poor patient compliance. Another reason for incomplete eradication is the probably that residence time of antimicrobial agents in the stomach is so short, that effective antimicrobial concentrations cannot be achieved in the gastric mucosa layer or epithelial cell surfaces where H. pylori[6]. Recently ornidazole is proved to be one of the potential drugs against H.pylori infection, responsible for peptic ulcers and various cytotoxic complications. This leads to the formulation of acceptable sustained-release dosage forms ornidazole in the stomach to promote a fast and effective eradication of H.pylori to cure pepticulcer[7]. So, In the present study an attempt is made with the main objectives of preparation and evaluation of insitu gelling system of ornidazole that retains in the stomach by adhering with gastric wall and provides an increased gastric residence time, resulting in prolonged drug delivery in gastro intestinal tract and increases local concentration of the drug effectively for complete eradication of H.pylori with better patients compliance.

MATERIALS AND METHODS

Materials

Ornidazole was obtained as a gift sample from Medo Pharma Limited, Karnataka. Sodium alginate was obtained as gift Sample from Applied Bioscience Consultants and Distributors Ltd, Mumbai and all other excipients used were of pharmaceutical grade.

Method of Preparation of Ornidazole in Situgel

Preparation of Sol

Gellan gum (0.5-2.0%w/v) solution was prepared with distilled water and stirred continuously with magnetic stirrer. Then sodium citrate (0.25%w/v), calcium chloride (0.016%w/v) is added heated to upto 60ºC for about 30mins, the prepared sol is allowed to cool then optimum quantity of Ornidazole and calcium carbonate (0.75%w/v) were added. This sol is stored in room temperature until further use[8] (Table No.1).

Evaluation pH measurement

The pH of the developed gel base was measured on a standardized digital pH meter at room temperature by taking adequate amount in a 50 ml beaker[9].

Viscosity and Rheology studies

Viscosity determination was carried out on Brookfield Viscometer (ModelNo.CAT200+) using spindle 62. Viscosity of *insitu* gelling solutions was measured at different angular velocities at a temperature of 37±1°C. A typical run comprised changing of the angular velocity from 0.5to100 rpm with a run time of 30sec. After completing the cycle with a similar wait at each speed the hierarchy of angular velocity was reversed (100rpm to 0.5 rpm) with a similar wait of 30sec. The absolute viscosity of formulations was reported at a fixed torque value. The averages of two readings were used to calculate the viscosity. The rheological behavior was explained by plotting viscosity against angular velocity[10].

***In-Vitro* Buoyancy study**

In Vitro Buoyancy study is characterized by floating lag time and total floating duration. *In Vitro* Buoyancy study of the solw as carried out using USP dissolution apparatus Type-II. The medium used was 900 ml of 0.1NHcl. The temperature of the bath and medium was maintained at 37±0.5^{o}C throughout the study. 10ml of the *insitu* gelling solution was transferred by using a syringe. Note the time required for gelled mass to rise to the surface of the dissolution medium [Floating Lag time] and the duration of the time for which the gel constantly floated on the dissolution medium [Floating duration] was noted for each formulation trial[11].

Measurement of water uptake by the gel

The water uptakes by the gel of the selected formulations of sodium alginate were determined by a simple method. In this study the in situ gel formed in 40ml of 0.1NHcl (pH1.2) was used. From each formulation the gel portion from the 0.1NHcl was separated and the excess Hcl solution was blotted out with a tissue paper. The initial weight of the gel taken was weighed and to this gel 10ml of distilled water was added and after every 30 minutes of the interval water was decanted and the weight of the gel was recorded and the difference in the weight was calculated and reported[12].

***In vitro* drug release study**

The release rate of ornidazole from sustained release formulation was determined using USP dissolution testing apparatus type-II at 50rpm. This speed was slow enough to avoid the breaking of gelled formulation and was maintaining the mild agitation conditions believed to exist *in vivo*. The dissolution medium was used 900ml of 0.1NHcl, and temperature was maintained at 37^{o}C. 5ml of solution containing the optimum quantity of sodium citrate, calcium chloride, in distilled water and loaded with drug was placed in petridish which was then float on dissolution media. Gelation was instaneous on contact with simulated gastric fluid. 1ml of sample of the solution was removed at pre-determined interval for analysis and replace with 1ml of fresh 0.1NHcl. The drug concentration of each sample was determined Spectrophotometrically[13].

Measurement of Gel Strength

The experiment was carried out according to the previously published methods. Twenty-five milliliters of the sols prepared were put into 50ml glass cylinder, which were placed into a water bath at 36°C for 5 min to allow for conversion to gel. A piston with eye holes in the surface was put into the cylinder; mean while, a weight (35g) was place to the piston to make it go down. The gel strength was determined as time taken to move the piston 5 cm down through the gel.

Gel strength was determined for sols containing sodium alginate[14].

Drug content estimation by spectrophotometric analysis

The gelled mass formed after coming in contact with 0.1NHcl into the matrix structure. This gelled mass is responsible for the sustained release of the drug from matrix structure as the wall of the gelled mass acts a diffusion controlling membrane. The inner core of the gel mass contains the drug in sol form that diffuses through this membrane. After the in vitro release studies are carried out for the

duration of 12hours certain amount of residual drug remains in the core of gelled mass. Thus to estimate this drug content the after gelled mass is transferred to 50ml of 0.1NHcl and crushed using a mechanical stirrer by overnight stirring, so as to get uniform dispersion. The resulting dispersion is then filter educing Whatmann filter paper. The resulting solution is then analyzed using UV spectrophotometer and quantity of Ornidazole is determined[15].

RESULTS AND DISCUSSION

Infrared spectroscopy

The IR spectra of ornidazole and ornidazole physical mixture with other excipients were illustrated into the Figure No.6, 7 and 8 respectively. Physical mixture showing almost similar identical IR ranges of pure drug which proves the compatibility of drug and used excipients i.e there is no interaction between drug and excipients (Figure No.1 and 2).

Evaluation of Gel Parameters pH measurement

All the formulations were showing pH in the range of 7.6-7.8 as shown in Table No.2. This is well in the range for orally administered formulation.

Therefore there is no need for adjusting pH.

In vitro floating study

Floating log time based upon the release of carbon dioxide from the formulation was observed as 170 sec for FB1 and 65 sec for FB4 and floating time observed more than 12 hrs for all formulation as shown in Table No.2.

Measurement of water uptake by the gel

Prepared all formulations exhibited water uptake which is observed in the range of 9-12%. Release of the drug from the polymer matrix depends on the amount of water extended period of floating lag time and drug release respectively. The Figure No.3 shows the floating ability of insitu gel of different concentration of gellan gum associated with the system. The release of the drug may involve the penetration of water into the matrix and simultaneously release of the drug via diffusion or dissolution. The water associated with the formulation at any point in the time can be determined by thermo gravimetric analyzer but in this present study a simple test was done for the selected batches of sodium alginate based *in situ* gel of ornidazole (Table No.2).

Gel strength (sec)

All formulations exhibited good gel strength which is observed in very low as 18.6 sec for FB1 and higher values are observed as increasing the concentration of gellan gum as 64.5 sec for FB4 (Table No.2).

Drug content (%)

Drug content for the prepared formulations was observed with high drug loading which is more than 90% showing maximum drug entrapment. Formulation FB1 (99.6%) selected as an optimized formulation (Table No.2).

Viscosity of Formulation

The rheological properties of the sols are importance in view of their proposed oral administration. In the selection of the concentration of the gelling compound, a compromise is sought between a sufficiently high concentration for the formulation of gels of satisfactory gel strength for use as a delivery vehicle, and a sufficient low concentration to maintain an acceptable viscosity for ease of swallowing. Below Figure No.4 and 5, and Table No.3 and 4 compares the shear dependency of the viscosity of the different gellan gum concentration.

The formulations without drug exhibited pseudo-plastic flow, as shown by shear thinning and a decrease in the viscosity with increased angular velocity. The sols showed a marked increase of viscosity with increasing concentration of polymer from the graph we can select the optimized concentration of polymer (0.5%) that is used for oral drug delivery.

The effect of polymer concentration on *In vitro* drug release from i*nsitu* gels showed decrease in the rate and extent of drug release was observed with the increase in polymer concentration. The releases of drug from these gels were characterized by an initial phase of high release (burst effect). However, as gelation proceeds, the remaining drug was released at a slower rate followed by a second phase of

moderate release. This bi-phasic pattern of release is a characteristic feature of matrix diffusion kinetics. The initial burst effect was considerably reduced with increase in polymer concentration. In the absence of calcium and sodium ions present in the formulation will be predominantly in ionized form and cause weak gelation. The dissolution medium used was 0.1NHcl (pH 1.2). The result of *In vitro* release of ornidazole from the formulation is given in Table No.5 and release profiles presented graphically in Figure No.8. However, the results clearly show that the gels have ability to retain the drug for prolonged periods. The graph indicates that as the concentration of polymer increases there is increase in drug release and vice-versa with sustaining the drug release.

***In vitro* release study**

From the results of above parameters, Batch FB1 was chosen for final treatment of evaluation. In case of drug release when concentration of polymer decreases it release the drug faster and when concentration of polymer increases it release the drug slower. So, I selected FB1 as a optimized formulation. It was giving drug release of 28.56 %,35.01%, 42.44%, 50.27%, 58.55%, 68,57%, 74.70% and 80.84%, 85.75%, 89.65% and 96.36% for 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h and 12h respectively proving sustained release of ornidazole from given combination of excipients. Viscosity is also considered as crucial factor for batch selection where FB1 showed viscosity of 9400 cPs before gelation and 6200cPs after gelation resulting into sol-gel transition with low viscosity before gelation so that it can be administered easily.

Floating time and floating lag time was also observed in good manner for sustaining drug effect. Whereas the formulation FB3 and FB4 having concentration (1.5%, 2.0%) of gellan gum showed maximum viscosity in solution forms as well as in gels form showed in Table No.5. If is also predictable that the formulation FB3 and FB4 having higher concentration of polymer were poor candidate for *insitu* formulation since it exhibited higher viscosity for solutions and hence were not pourable (Figure No.6).

Table No.1: Formulation code for insitu gelling formulation with Gellan gum

S.No	Ingredients (%)	FB1	FB2	FB3	FB4
1	Ornidazole	0.5	0.5	0.5	0.5
2	Gellangum	0.5	1.0	1.5	2.0
3	Sodium Citrate	0.25	0.25	0.25	0.25
4	Calcium Chloride	0.016	0.016	0.016	0.016
5	Calcium carbonate	0.25	0.5	0.75	1.0

Table No.2: Evaluation of formulated batches FB1 and FB4

S.No	Formulation code	pH measurement	Floating lag time in sec	Floating time in hrs	Water up take study in 2hrs	Gel strength in sec	Drug Content (%)
1	FB1	7.6	170	<11	11.62%	18.6	99.96
2	FB2	7.5	127	>12	10.88%	32.2	100.84
3	FB3	7.8	93	>12	10.12%	46.6	97.64
4	FB4	7.6	65	>12	9.62%	64.5	99.78

Table No.3: Viscosity for oral insitu gel formulation (FB1-FB4) before gelling

S.No	RPM	Viscosity before gelling (cps)			
		FB1	FB2	FB3	FB4
1	0.5	9400	13950	19500	25000
2	1	8690	12800	18400	23500
3	2.5	7240	10600	16500	21000
4	5	6300	8300	14000	19000
5	10	5200	7500	11300	15730
6	20	3150	5200	9200	12300
7	50	1500	2700	6800	9740
8	100	800	1450	3000	4450

Table No.4: Viscosity in cps for oral insitu gel formulation (FB1 –FB4) after gelling

S.No	RPM	Viscosity after gelling (cps)			
		FB1	FB2	FB3	FB4
1	0.5	6200	36000	63000	86000
2	1	5700	28000	45000	66000
3	2.5	4800	23000	41000	62000
4	5	4500	20100	38000	58000
5	10	4150	17000	34000	54000
6	20	3800	14000	30000	49000
7	50	3400	10500	24000	43000
8	100	1900	6200	15000	22000

Table No.5: *In vitro* drug release study of FB1, FB2, FB3, FB4

S.No	Time	Cumulative release (%)			
		FB1	FB2	FB3	FB4
1	0	0	0	0	0
2	1	28.56±0.46	26.86±0.58	25.75±0.76	26.76±0.68
3	2	35.31±0.50	33.75±0.64	32.01±0.64	33.31±0.59
4	3	42.44±0.63	40.71±0.67	38.54±0.84	36.38±0.56
5	4	50.27±0.68	49.40±1.08	42.04±0.90	40.31±0.19
6	5	58.55±0.57	56.82±0.54	52.04±0.89	42.95±0.79
7	6	68.57±0.57	64.23±0.30	57.29±0.77	44.30±0.71
8	7	74.70±0.65	67.77±0.45	63.85±0.83	46.94±0.83
9	8	80.84±0.92	70.44±0.54	66.08±0.72	49.59±1.01
10	9	85.75±0.92	76.67±0.74	71.54±0.82	53.34±0.58
11	10	89.65±0.68	80.45±0.85	73.39±0.54	57.81±0.37
12	12	96.36±0.83	87.71±0.68	76.52±0.72	68.50±0.54

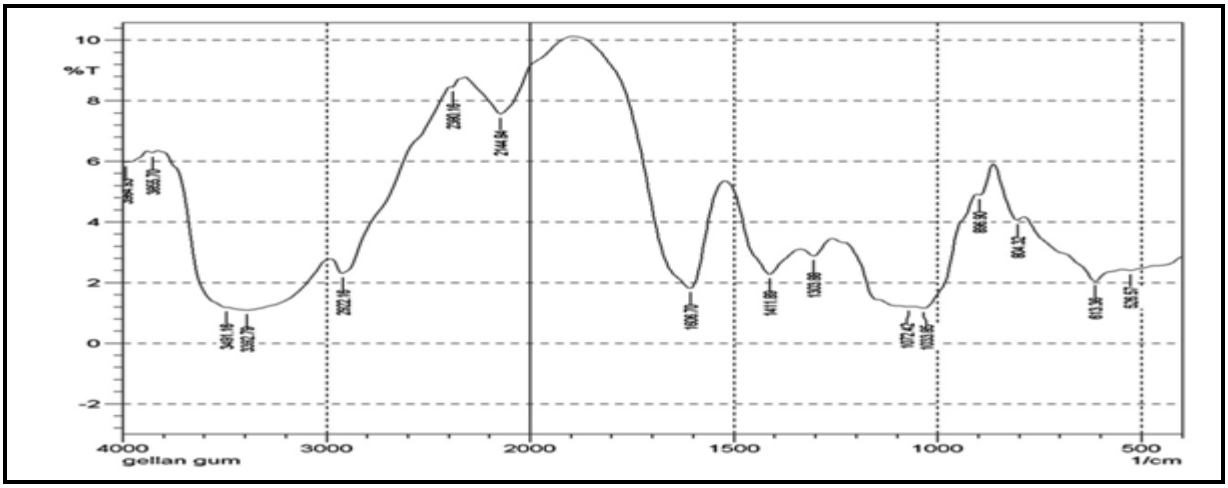

Figure No.1: FTIR spectra of Gellan gum

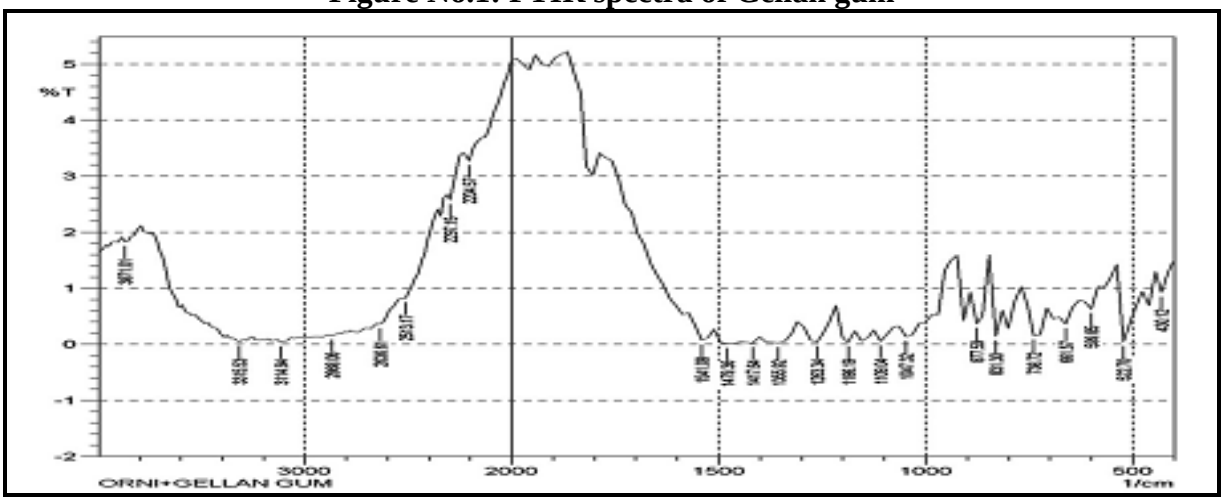

Figure No.2: FTIR spectra of Ornidazole + Gellan gum

Ornidazole *insitu* gel with 0.5% (FB1)

Ornidazole *insi u* gel with 1.0% (FB2)

Ornidazole *insitu* gel with1.5% (FB3)

Ornidazole *insitu* gel with 2.0% (FB4)

Figure No.3: Formulation of insitu gelling solution by using Gellan gum

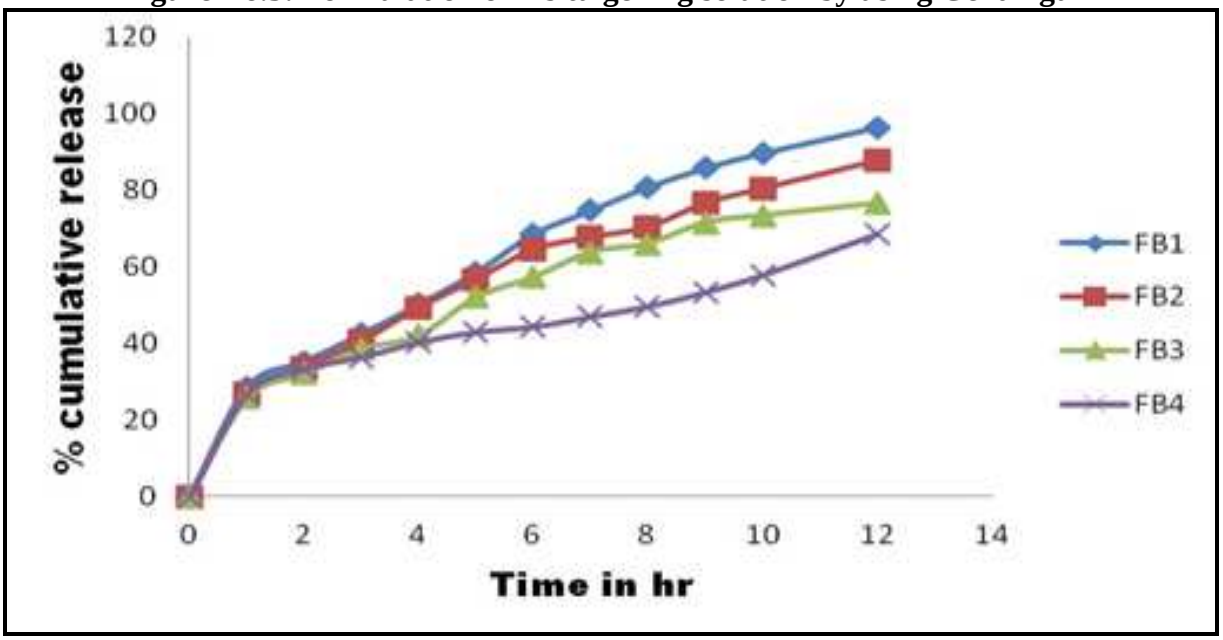

Figure No.4: Percentage cumulative drug release of FB1-FB4

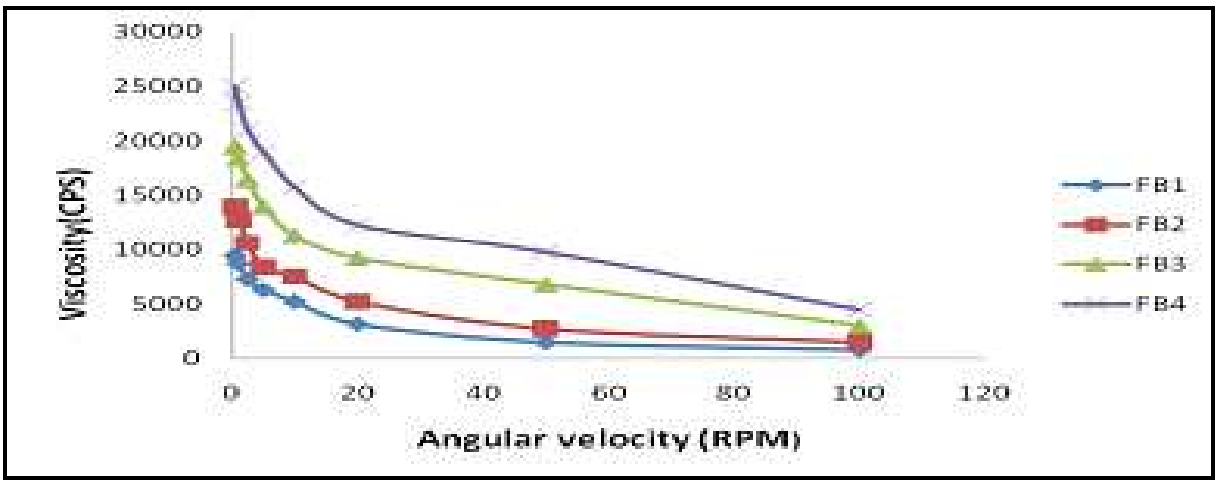

Figure No.5: Viscosity of formulation FB1-FB4 using Gellan gum before gelation

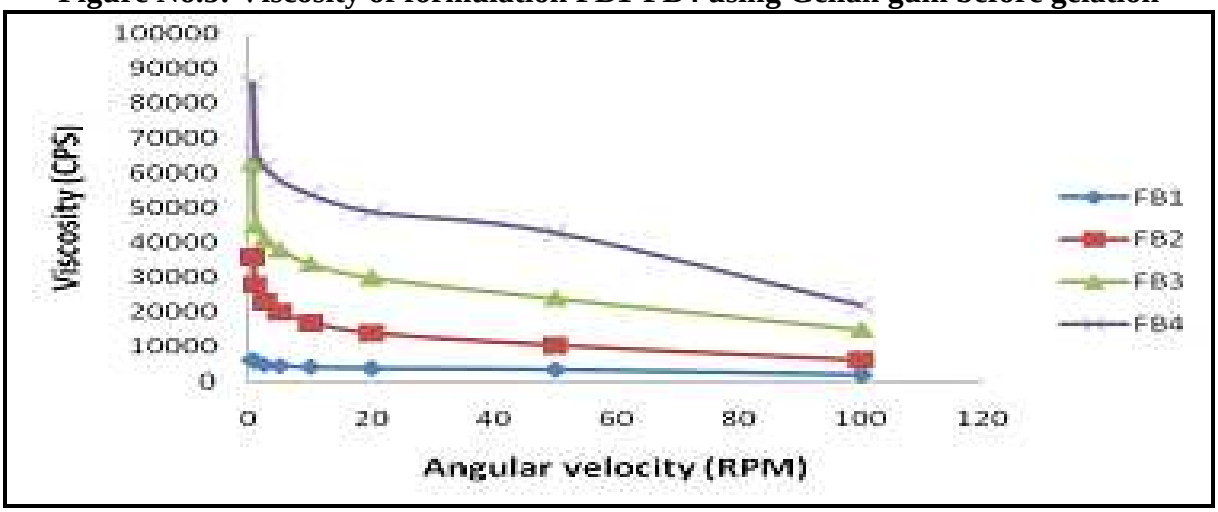

Figure No.6: Viscosity of formulation FB1-FB4 using Gellan gum after phase transition

CONCLUSION

The formulated *in situ* gel for ornidazole was found to be easier and simpler, to produce stable in *situ gel*. It was found to have better floating efficacy and *in vitro* release profile characteristics. Hence it may represent as a new alternative biodegradable and cheaper formulation of ornidazole which may improve the patient compliance and sustained release.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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