Field of the invention:

The present invention relates to a extended release oral formulation of a broad spectrum macrolide antibiotic such as mainly Clarithromycin by the use of a unique blend of polymer matrix.

More particularly, the present invention relates to a unique sustained/extended release oral formulation using a blend of polymer matrix system for treating specifically Gastro-esophageal reflux disease (GERD), Chronic gastritis, Gastric ulcer etc. related with H. pyloric infection as those infections needs to be inhibited based on a extended release profile of the antibiotic such as mainly Clarithromycin.

Background of the invention:

Clarithromycin is a semi-synthetic macrolide antibiotic that inhibits bacterial protein synthesis. It is more acid-stable, better absorbed, and is widely used as a component of anti-*Helicobacter pylori* (*H pylori*) regimens along with other therapeutics.

Macrolide antibiotic such as mainly Clarithromycin is effective against a number of organisms and are generally administered 2-3 times a day as immediate release dosage form. As Log P value of Clarithromycin is 3.18 (lipophilic), it is rapidly absorbed by GIT membrane (Gastro Intestinal Track), after its dissolution in the stomach environment in case of immediate released dosage form. As a result of such phenomenon, peak plasma concentration is achieved quickly that leads to different side effects like diarrhoea, nausea, extreme irritability, abdominal pain and vomiting, facial swelling . To avoid such complications extensive research has been done to formulate the control or extended release dosage form of clarithromycin.

One of such references is made in the US Patent 4842866 assigned to Abbott Laboratories where the frequency and duration of the administration and/ or the adverse effects related to Clrithormycin administration in the gastrointestinal disorders was shown. Moreover the same patent clearly shows that reproducibly bioavialable dosage form comprising clarithromycin could not be produced.

In a another reference described in US patent 5705190 assigned to Abbott , clearly shows that the incorporation of an organic carboxylic acid such as citric acid was used mainly to increase the bioavialability of the erythromycin derivative (i.e clarithromycin) in once a day dosage forms, bioequivalent to the marketed immediate release twice daily composition. However, this compositions exhibited maximum plasma concentrations (C max), there by failing to minimize the adverse effects relating to gastrointestinal disorders including nausea, vomiting & taste perversion .

Yet another reference may be made to US Patent 6010718 assigned to Abbott, discloses a method for preparing controlled release matrix tablet formulation (500 mg tablet weighing about 1000mg) comprising from about 5% to 50% by weight of a pharmaceutically acceptable polymer . The tablet formulation comprising 10, 20, & 30% by weight of low viscosity hydroxypropylmethylcellulose (polymer). But it was observed that the percentage mixture of the polymer that was taken, was not accurate to give the targeted result to induce statistically lower mean fluctuation index in the plasma than an immediate release composition of the erythromycin derivative while being substantially bioequivalent to the immediate release composition.

Like wise another reference may be made to International patent publication number WO0149246 A2 assigned to L. Oner & A. Toksoz which discloses a pharmaceutical compositions comprising from about 3% to about 40% by weight of hydrophilic hydroxyalkylcellulose. It also failed to achieve the desired release profile as per U.S.P guideline is concern.

A further reference may be made to US Patent Publication No. US2001094170 20010829 with the publication date of June 27th, 2002, which relates to control release pharmaceutical composition comprising of about 0.1% to about 4% by weight of one or more pharmaceutically acceptable dissolution rate controlling polymers, such as carbohydrate gums, polyuronic acid salts, cellulosic ethers, acrylic acid polymers and mixtures thereof.

But it was observed that the percentage mixture of the polymer which was taken was not accurate to give the targeted result for a extended period of time.

In a literature on 'Drug utilization of clarithromycin for gastrointestinal disease treatment' by Quan Zhou et el. , published in '*World J Gastroenterol* 2008 October 21; 14(39): 6065-6071' , clearly showed the improved quality of clarithromycin sustained release formulation especially with regard to administration schedule, concordance between indications and diagnoses and management of drug interactions associated with *H pylori* induced infections. Here the author always preferred an extended release formulation of Clarithromycin for the effective management of *H pylori* induced infections specifically Gastro-esophageal reflux disease (GERD), Chronic gastritis, Gastric ulcer etc.

In view of the above citations, the oral clarithromycin formulations available in the market include immediate-release (IR) clarithromycin and sustained or extended-release (SR/ER) clarithromycin. The two formulations have different administration schedule, clinical indications and therapeutic cost.

The two formulations have different administration schedule, clinical indications and therapeutic cost. The SR Clarithromycin has obvious advantages over the IR (immediate release) product when they are prescribed for the same indications. These advantages are as follows:

1. higher antimicrobial activity as SR clarithromycin proved to be a time-dependent antibiotic for its extended drug release pattern;
2. better tolerability, fewer gastrointestinal adverse reactions and reports of abnormal taste;
3. bioequivalance between the SR (1000 mg *qd*) and IR (500 mg *bid*); and
4. enhanced medication compliance due to its convenience.

But what percentage of polymer should be used in a SR or ER Clarithromycin formulation to achieve a extended term drug release profile (approx. 12 hours as per U.S.P), is nowhere mentioned in the prior art.

In view of the existing prior art, the present invention leads to a formulation for preparing an extended release oral dosage form of 500mg Clarithromycin. More particularly the present invention uses a unique blend of polymer matrix system as a base for retarded or extended release of the macrolide antibiotic i.e Clarithromycin and thereby solves all the drawbacks of existing prior arts.

Objects of the invention:

The main object of the present invention is to provide an extended release oral formulation of a broad spectrum macrolide antibiotic such as mainly Clarithromycin.

Yet another object of the present invention is a method for preparing a unique blend of polymer matrix system as a base for the retarded release of the Clarithromycin drug.

Still another object of the present invention is to establish the facts on a theoretical basis that such unique Clarithromycin formulation, using an unique blend of polymer matrix, can be used for the effective management of *H. pylori* induced infections specifically Gastro-esophageal reflux disease (GERD), Chronic gastritis, Gastric ulcer etc., which requires a extended drug release pattern.

Summary of the invention:

The present invention provides an extend/sustained release pattern of oral formulation of Clarithromycin using an unique blend of polymer matrix system, for achieving such formulation, that is used as a base for retarded release of the drug. Different grades of hydroxypropylmethyl cellulose (HPMC) are mixed in different ratio to obtain a suitable matrix for such extendede release of the said macrolide antibiotic i.e Clarithromycin. Magnesium stearate is used as lubricant in certain concentration and a high grade viscosity of the HPMC mixture, which is acting as a binder, is used in the tablet formulation of the said antibiotic drug. To retain the dosage form in the stomach for a sustained period of time (upto 12 hours as per The United States Pharmacopoeia), floating mechanism is applied.

Detailed description of the invention:

The present invention leads to a method for preparing an extended release tablet formulation of 500mg clarithromycin. A unique blend of matrix system is used as a base for retarded release of drug. Two different grades of hydroxypropylmethyl cellulose (HPMC) as a polymer are mixed in optimized ratio of 1:21 (HPMC **K4M** : HPMC **K15M)** to obtain a suitable matrix system for achieving the extended release profile of the said macrolide antibiotic i.e Clarithromycin.

Statistical analysis is done based on 14 different formulations (TABLE 1) where different percentage of HPMC **K4M,** HPMC **K15M** and $NaHCO_3$ are taken to obtain the following results :

TABLE 1 Optimization of Data Sheet as supported by Statistical analysis

Formulation	HPMC K4 M (%)	HPMC K15M (%)	$NaHCO_3$ (%)	FLT (min)	TFT (min)	CPR 2h (%)	CPR4h (%)	CPR 8h (%)	CPR12h (%)
1	9.333333	16	20.66667	2	13	18.43	35.43	74.89	91.85
2	0	24	22	1	15.9	16.21	31.06	62.21	81.04
3	28	0	18	3	11.6	30.1	49.72	83.48	100.53
4	6	20	20	1.5	12.5	17.93	33.67	67.42	90.35
5	20	0	26	3	12	27.79	45.03	79.78	97.75
6	0	28	18	3	15	15.69	30.02	60.4	78.52
7	14	14	18	3.1	12	20.72	36.03	76.07	95.85
8	28	0	18	3	12	29.53	50.02	82.9	99.48
9	0	20	26	0.8	13	17.03	33.03	67.31	90.25
10	13.33333	6.666667	26	0.8	12	22.34	36.73	76.59	95.75
11	24	0	22	1	12	28.91	46.54	80.71	99.03
12	0	20	26	0.9	13	15.65	34.03	65.98	92.04
13	0	28	18	2.9	16	15.03	31.36	59.89	79.99
14	18.66667	9.333333	18	2.5	12.4	24.8	40.82	77.98	97.42

Based on the above batch analysis, the final optimized percentage of the polymers (i.e. HPMC **K4M & K15M**), $NaHCO_3$ and other excepients are taken here (TABLE2) in our Clarithromycin formulation in the following manner to achieve an extended drug release pattern:

Clarithromycin(%)	HPMC K4M (%)	HPMC K15M (%)	$NaHCO_3$ (%)	Citric Acid (%)	Mg-Stearate (%)
50	1	21.538437	23.456961	3	1

TABLE 2

So for obtaining the above optimized value, at first all ingredients (HPMC K4M, HPMCK 15 M, Drug. NaHCO3) are mixed by geometric dilution. Citric acid is dissolved by 4 ml ethanol in a petridis. Then the mixture is mixed with the citric acid associated with ethanol to prepare a kindle like mass. Then Granules are prepared by 16 mesh and subsequently followed by 24 mesh sieve. After that the granules are subjected to drying in hot air oven until 5% moisture retains. After optimum drying the prepared granules are ready for punch in tablet punching machine.

As other excepients, citric acid and magnesium stearate are used to achieve the optimum formulation. Magnesium stearate is used as lubricant in certain concentration which does not affect the desirable release of drug. High grade viscosity of the HPMC mixture is acting as a binder in the tablet formulation of the said antibiotic drug. To retain the dosage form in the stomach for a sustended or extended period of time, floating mechanism is applied. Sodium bicarbonate ($NAHCO_3$) is used in different concentration to get the optimal floatability i.e. floating lag time (FLT) & total floating time (TFT) of the antibiotic Clarithromycin tablet. From the experiment it is clear that Sodium Bicarbonate does not have any direct effect on drug release profile. To enhance the floating ability of the formulation by maintaining additional acidic pH, particularly in case of severe H. pyloric infection in stomach where the pH is on the basic side, a fixed concentration of citric acid, which has very slight effect (less than 0.1%) on drug release profile, is used. Ethyl alcohol is used as granulating fluid.

Finally the prepared Clarithromycin tablets are evaluated for the weight variation test, thickness and hardness. The weight variation, thickness and hardness values showed no significant difference from the average value. The friability is also within the specified limits. The drug content in all the formulations of Clarithromycin tablets are within the range of 95 to 105%.

Moreover the present invention also describes a unique blend of polymer matrix system for achieving a Clarithromycin tablet formulation which shows an extended drug release profile in the in-vitro environment as supported by USP (The United States Pharmacopoeia). As per USP reference (U.S.P Edition- 2009, Volume: II, Pages: 1957, 1959 and 1961), the dissolution profile of an extended/delayed release tablet of clarithromycin must follow the below mentioned profile :

Sl. No.	Time (hour)	% dissolved
1	2	Not more than 25
2	4	20-40
3	8	45-75
4	12	Not more than 80

So to achieve the above USP dissolution/release pattern, Clarithromycin release study is performed by using USP dissolution test apparatus Type II (paddle method) using 900 ml of 0.1N HCl at 37 ± 0.5°C at 50 rpm. This study was done for 12 hrs. A sample of 5 ml are withdrawn at an interval of 2hr,4hr, 8hr,12hr respectively. The samples are replaced with fresh dissolution medium each time. The samples were filtered through 0.45 trn membrane filter. The resultant samples are analyzed at 272 nm against reagent blank.

Response	'Targeted , Predicted & Obtained' responses for optimized floating time and Drug release pattern		
	Optimized formula		
	Target	predicted	**Obtained**
FLT(min)	0.8	0.6	0.65
TFT(hour)	12	14	13.5
CPR2h(%)	15.00	16.30	16.00
CPR4h(%)	30.00	32.41	32.50
CPR8h(%)	60.00	60.00	60.00
CPR12h(%)	90.00	87.04	88.00

TABLE 3

As per optimal floatability and drug release pattern of the Clarithromycin tablet formulation is concern we follow the above mentioned data table, where **TABLE 3** shows our final experimentation result. Here in the **'obtained'** column, with respect to a predetermined 'target' and software oriented 'predicted' values are concern, we are successfully able to obtain the almost exact amount of an extended/delayed release profile of Clarithromycin oral formulation as supported by USP guideline.

The in vitro dissolution study in the present invention clearly shows that floating Clarithromycin tablet absorbed the water and got swollen. Initially a barrier gel layer formed around the tablet and the interior of the tablet remained dry. The drugs diffused through this barrier gel layer. This gel layer gradually eroded with time & release of the drug over a extended period of time upto 12 hours to achieve its targeted results which are necessary for infections mainly associated with H. pylori.

Brief description of the drawings:

According to different analytic study, mainly FTIR (Fourier transform infrared spectroscopy) and DSC (Differential scanning calorimetry) as mentioned in the drawing, it is concluded that there is no physical or chemical interaction is found between our unique polymer blend (i.e, HPMC K4M & K15M), drugs and other excepients in our extended release formulation of Clarithromycin wherein :

Fig.1 , represents the DSC (Differential scanning calorimetry) curve of pure Clarithromycin.

Fig.2 , represent DSC curve of the present formulation of Clarithromycin as mentioned here in the invention.

Fig.3 , represents the FTIR spectra of pure Clarithromycin.

Fig.4 , represents the FTIR spectra of the present formulation of Clarithromycin.

Fig.5 , represents the in-vitro drug release pattern of the present extended release antibiotic formulation of Clarithromycin.

Detailed Description of the preferred embodiments:

These and other features, aspects, and advantages of the present invention will become better understood when the following detailed description is read with reference to the accompanying drawings as mentioned above wherein:

Fig.1 represents the DSC (Differential scanning calorimetry) curve of only pure Clarithromycin (available in market), where red curve shows the general melting point (M.P) & green curve or the TG (Thermo gravimetric) curve is showing dehydration of the pure Clarithromycin. DSC curve is plotted against 'Heat flow' Vs 'Temperature' and the TG curve is plotted against '% of weight loss' Vs 'Temperature'. Temperature range on the DSC of the red curve, starts from 36 Degree Celsius & ends in to 307 Degree Celsius. Temperature has been taken up to 307 Degree Celsius because the melting point of the pure Clarithromycin is in the temperature range between 217°C-220°C. Here, the range of heat flow on DSC plot is between -7.698 mW to 9.003 mW.

There are two deflections on the DSC curve (red). One is on the range of 220°-225° Celsius & other is on the range of 285°-300° Celsius region. The two deflections indicate that in this positions endothermic reaction have been occurred and the pure Clarithromycin sample absorbs heat. There are two reasons for the absorption of heat by the sample. One is , the pure sample melts by absorbing heat & other is the pure sample becomes dehydrated by absorbing heat. Now we have to understand, which peak is for melting point & which peak indicates dehydration. By two ways we can solve it. Since the first endothermic peak is sharp than the second, so first one is for the melting of the pure sample and the second peak is for dehydration. As this is further supported by the help of TG curve (green) because in the second peak region, the deflection of the TG curve indicates weight loss of the pure sample. That means in this temperature region (285-300 Degree Celsius) sample loose its crystal water & becomes dehydrated.

We can conclude that the first endothermic peak (in between 220°C-225°C) is for the melting point & the second endothermic peak (in between 285° C-300° C) indicates the dehydration temperature of the pure Clarithromycin sample. Therefore if our Clarithromycin formulation on the DSC curve shows the same endothermic peaks at the same temperature regions, then we will confirm that the melting point of Clarithomycin drug in our formulation remains unchanged & no physical interaction occurs between the drug and excepients during formulation.

Fig.2 represents the DSC curve of our 'optimized formulation'(as mentioned in TABLE2) of Clarithromycin tablet, where again red curve & green curve or the TG (Thermo gravimetric) curve is showing the melting point (M.P) and dehydration respectivel of our Clarithromycin formulation as described in the present invention. Temperature in the DSC plot starts from 30 Degree Celsius and ends in to 319 Degree Celsius and the range of heat flow is in between -2.113mW to13.75 mW . Like the Fig.1, the Fig.2 also shows two deflections (i.e. endothermic peaks) on the DSC curve. One is on the range of 220°-225° Celsius & other is on the range between 285° C-300° C.

Since the position of the endothermic peaks of the two figures (Fig.1 and Fig.2) of the DSC plots are same in respect of temperature. So we can concluded that that the melting point of Clarithromycin in our formulation remains unchanged while using a unique blend of polymer matrix system. Moreover no physical interaction occurs between the drug and excepients during the present extended release antibiotic formulation of Clarithromycin.

Again to confirm whether there is any chemical interaction between drug (Clarithromycin) & other excipients during our formulation process as mentioned in the invention, we have done FTIR(Fourier Transform Infra red Spectra) study in Fig.3 and Fig.4.

In Fig.3 it shows, the FIIR of pure Clarithromycin(available in market). The graph is plotted against '% Transmittance (% T)' Vs 'Wave number (/ Cm)'. The range of Wave number is taken between a range from 348 Cm^{-1} to 7800 Cm^{-1} & the range of % T is between

'0 to 110' Degree Celsius. From this FTIR curve we can see 12 principle peaks of pure drug have been obtained in the following wavelength positons :

Peaks No.	Wavelength Position	Intensity (%T)
1	3471.24	42.195
2	2972.73	23.3542
3	2936.09	30.1419
4	1728.87	40.8242
5	1690	56.7079
6	1457.92	36.2826
7	1374.03	37.3331
8	1283.39	56.7645
9	1171.54	12.7498
10	1054.87	12.7132
11	1007.62	17.8074
12	0897.701	69.8217

Therefore if our Clarithromycin formulation on the FTIR curve shows all of the above principle peaks in a standard FTIR plot as mentioned in Fig.4, then it will automatically confirm that no chemical interaction occurs during present formulation of Clarithromycin.

So, Fig.4 here represents the FIIR data of the our Clarithromycin formulation as mentioned in the invention. The graph is plotted on the same scale as depicted in Fig.3. From Fig.4, it is prominent that all principle peaks of pure drug which are on the Fig.3 are still present in Fig.4. So we can conclude that there is no chemical interaction between drug & excepients during the present extended release antibiotic formulation of Clarithromycin.

Fig.5 shows the in-vitro drug release pattern of the present extended release antibiotic formulation i.e, Clarithromycin where the drug release pattern in dissolution medium is supported by U.S.P (United States Pharmacopoeia) (Reference :U.S.P Edition- 2009, Volume: II, Pages: 1957, 1959 and 1961).

The graphical plot represents 'Time Vs Cumulative percentage release' of present formulation. From this plot it is concluded that the formulation is able to extend or delayed its drug release effect for a span upto 12 hours which is also full filling as our targeted release specification (TABLE 3). More over the 'cumulative percentage release'(CPR) of the present Clarithomycin (antibiotic) formulation over time interval i.e, CPR2h(%), CPR4h(%), CPR8h(%), CPR12h(%) are respectively 16 %, 32.50 %, 60 % and 88 %. These results are completely supported by the U.S.P guide line (Reference :U.S.P Edition- 2009, Volume: II, Pages: 1957, 1959 and 1961) for considered to be an absolute extended release antibiotic i.e Clarithromycin formulation which is being obtained in the present invention with the help of a unique blend of polymer matrix system.

We Claim:

1. An extended release formulation of a broad spectrum macrolide antibiotic such as mainly Clarithromycin which comprising:
   a unique blend of polymer matrix, $NaHCO_3$ (Sodium bicarbonate) and other excepients in a optimized ratio (as mentioned in TABLE2) to achieve an extended or delayed drug release profile upto 12 hours without any chemical interaction between drug & excepients. Moreover due to this extended drug release profile of the present Clarithomycin formulation, it is easier to establish the facts on a theoretical basis that our Clarithromycin formulation, using an unique blend of polymer matrix, can be used for the effective management of *H. pylori* induced infections.

2. A unique blend of polymer matrix, as mentioned in Claim1, is using two different grades (K4M-low viscosity and K15M-high viscosity) of 'hydroxypropylmethyl cellulose' (HPMC) as a polymer which are mixed in optimized ratio of 1:21 (HPMC **K4M** : HPMC **K15M)** to achieve a optimum viscosity that helps to reach the targeted drug release profile (TABLE3) for extended period of time as mentioned in U.S.P guideline.

3. The extended drug release profile as mentioned in Claim2, is shown in Fig.5 where the 'cumulative percentage release'(CPR) of the present Clarithomycin (antibiotic) formulation over time interval proves that our results (i.e , CPR2h(%), CPR4h(%), CPR8h(%), CPR12h(%) are respectively 16 %, 32.50 %, 60 % and 88 %) are completely supported by the U.S.P guideline (U.S.P Edition- 2009, Volume: II, Pages: 1957, 1959 and 1961) for considered to be an absolute extended release antibiotic i.e Clarithromycin formulation which is being obtained in the present invention with the help of a unique blend of polymer matrix system.

4. The optimized ratio of unique blend of polymer matrix, as mentioned in Claim2, also ensures that no physical and chemical interaction occurs between drug (Clarithromycin) & other excipients during our formulation process as mentioned in the present invention and is further supported by DSC and FTIR analysis. Comparing Fig.1 and Fig.2 of DSC curve, it is concluded that the melting point of Clarithromycin in our formulation remains unchanged while using a unique blend of polymer matrix system. Moreover no physical interaction occurs between the drug and excepients during the present extended release antibiotic formulation of Clarithromycin. Whereas comparing Fig.3 and Fig.4, it is prominent that all principle peaks of pure drug which are on the Fig.3 are still present in our Clarithromycin formulation as shown in Fig.4. So it is established that there is no chemical interaction between drug & excepients during the present extended release antibiotic formulation of Clarithromycin.

5. $NaHCO_3$ (Sodium bicarbonate) as mentioned in Claim1, is used in the present tablet formulation of Clarithromycin as a floating agent where $NaHCO_3$ helps to retain the tablet dosage form of Clarithromycin by maintaining a optimized floating lag time (FLT) & total floating time (TFT) in the stomach, without disturbing the drug release profile.

6. As other excepients as mentioned in Claim1, citric acid and magnesium stearate are used to achieve the optimum formulation (TABLE2). Magnesium stearate is used as lubricant in optimum concentration which does not affect the desirable release rate of drug and a fixed concentration of citric acid is used.

7. The Clarithromycin formulation, as mentioned in Claim1, is used to prepare Clarithromycin tablets which are evaluated for the weight variation test, thickness and hardness without showing any significant difference from the average value. The friability is also within the specified limits. The drug content in the optimized formulation of Clarithromycin tablets are within the range of 95 to 105%.

Dated this 19th Date of May, 2009.

1. Swarnendu Bag
Signature
SWARNENDU BAG
(Name of the Signatory)

2. Amitava Chakraborty
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AMITAVA CHAKRABORTY
(Name of the Signatory)

ABSTRACT

An Extended Release Antibiotic Formulation Using Polymer Matrix System

An extended release formulation of a broad spectrum macrolide antibiotic such as mainly Clarithromycin which is comprising of a unique blend of polymer matrix, $NaHCO_3$ (Sodium bicarbonate) and other excepients in a optimized ratio to achieve an extended drug release profile upto 12 hours without any chemical interaction between drug & other excepients. Moreover due to this extended drug release profile of the present Clarithomycin formulation, it is easier to establish the facts on a theoretical basis that our Clarithromycin formulation, using an unique blend of polymer matrix, can be used for the effective management of *H. pylori* induced infections.

Name of Applicants:
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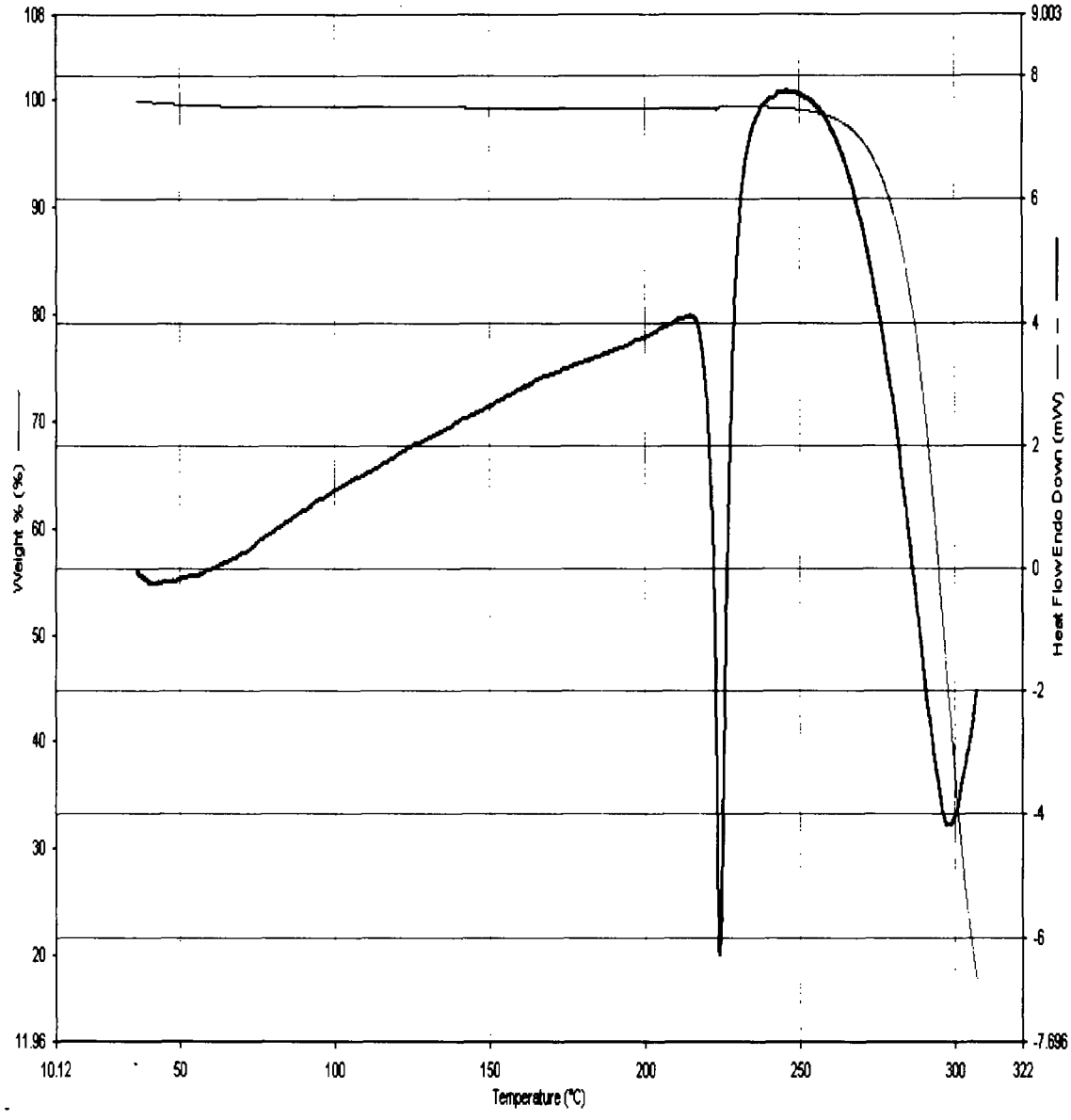

FIG. 1

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Signature of Applicants

Name of Applicants:
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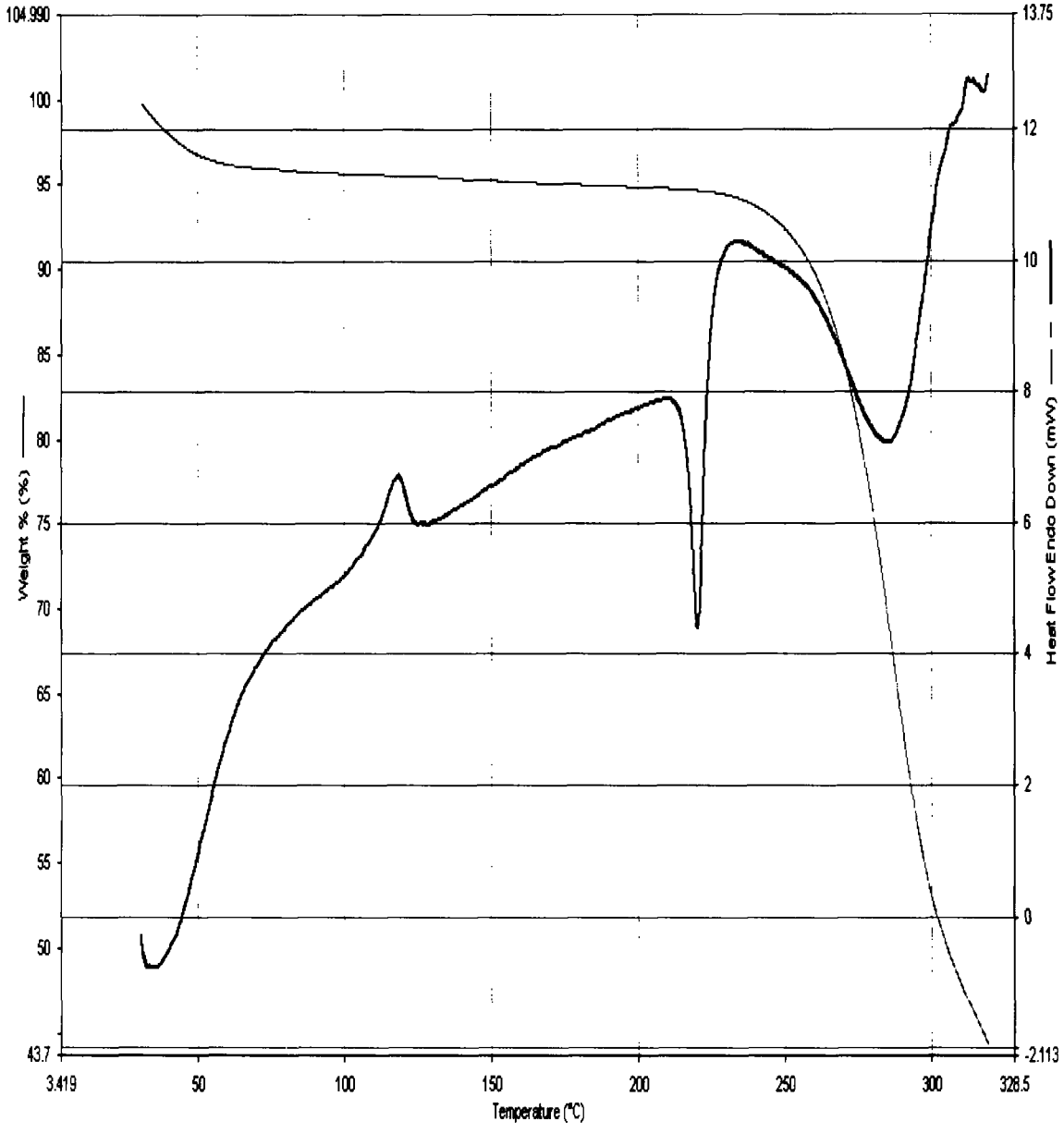

FIG. 2

1. Swarnendu Bag
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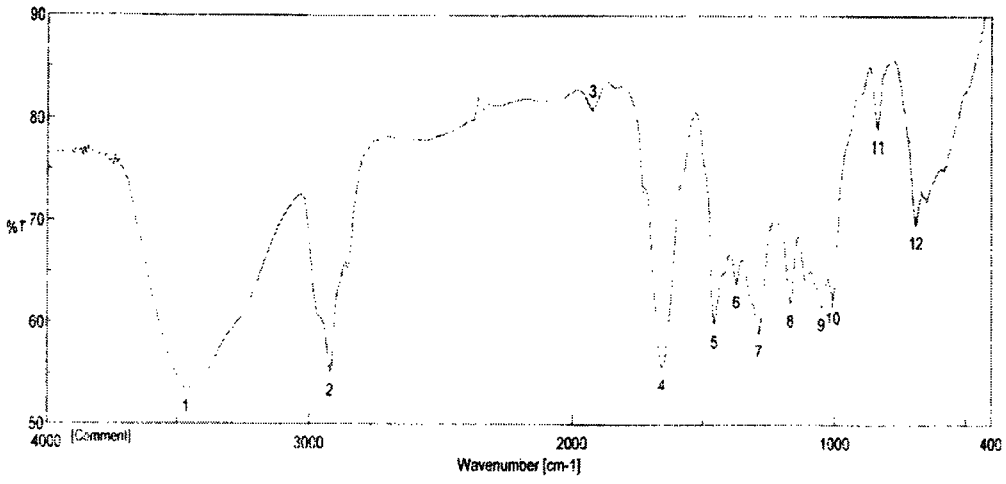

FIG. 3

1. Swarnendu Bag
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Name of Applicants:
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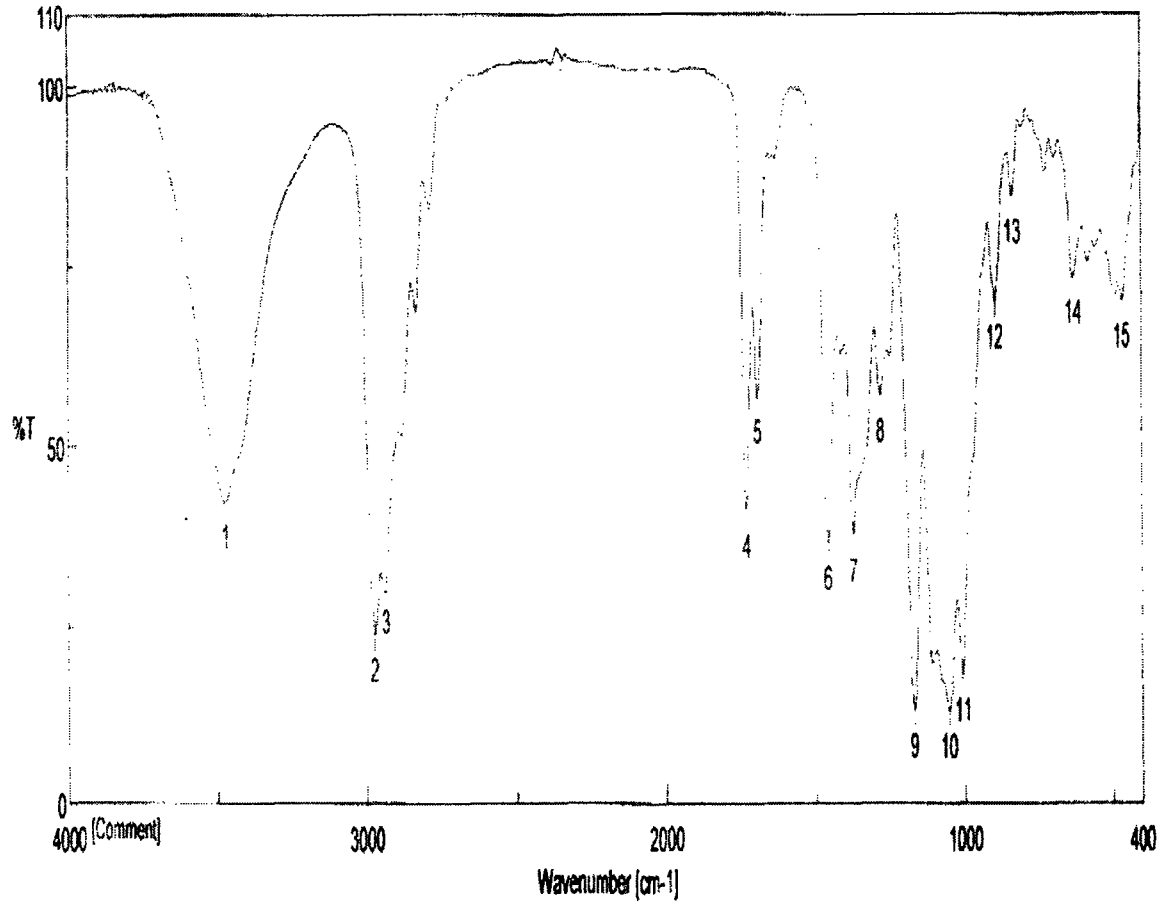

FIG. 4

1. Swarnendu Bag
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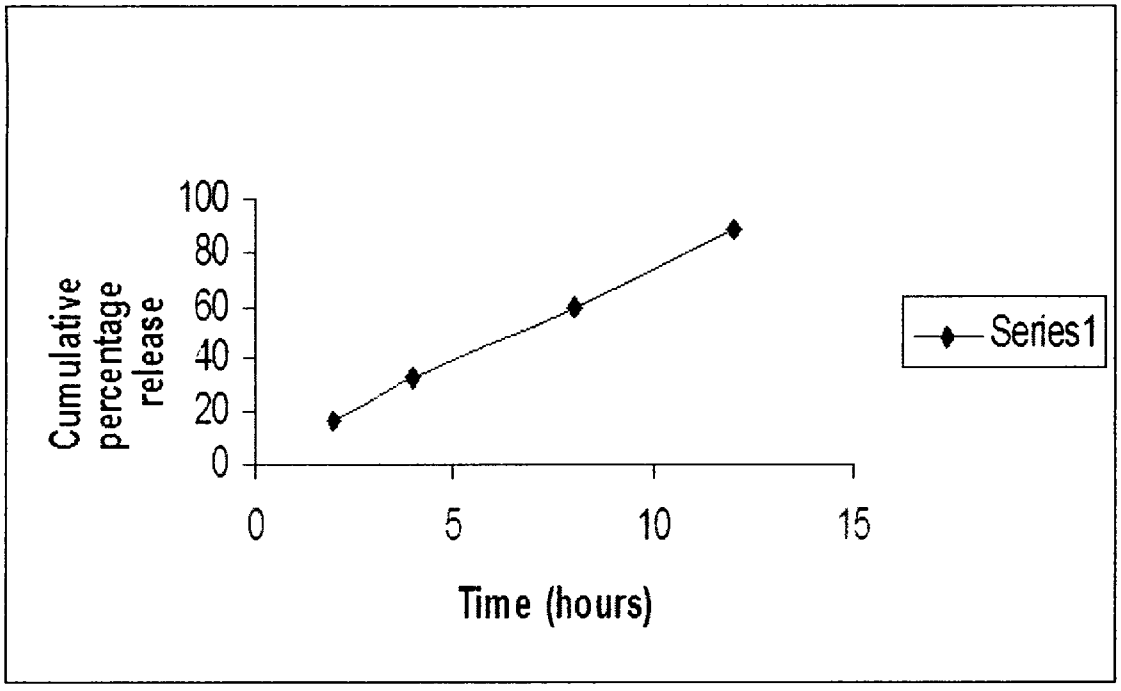

FIG. 5

1. Swarnendu Bag
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