Research Article

Indian Journal of Science and Research

Dubey A. & Ahirwar P., Ind. J. Sci. Res. 2022, 2(4), 78-86

ISSN 2583 – 2913

FORMULATION AND EVALUATION OF FLOATING MICROSPHERES IN COMBINATION OF AMOXICILLIN AND SUCRALFATE

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Abstract Drug delivery to the site of residence in the gastric mucosa may improve efficacy of the current and emerging treatments. Gastric retentive delivery systems potentially allow increased penetration of the mucus layer and therefore increased drug concentration at the site of action. Antibiotic resistance needs to be taken into account when designing treatment for *Helicobacter pylori* infection. Over the past decade many different therapies were promoted and recommendations changed rapidly. Most doctors lost track, and a great variety of treatments is being used. This study is a scientific approach for preparing a floating microsphere which is a serves as combination therapy of a Cytoprotective drugs Sucralfate and anti *H. pilory* drug i.e. Amoxicillin.

Key Words: Sucralfate, *H. pillory*, Amoxicillin, gastric, efficacy.

Introduction*:* Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the delivery of drugs. The primary objectives of any drug delivery system are to ensure safety and enhancement of efficacy of drug with improved patient compliance. The oral route has achieved the most attention and is quite flourishing. This is because of the simplicity of administration as well as the fact that gastrointestinal (GI) physiology offers more flexibility in dosage-form design than most other routes.[1] The development of oral drug-delivery systems for a specific drug involves the optimization of the dosage form and characteristics of GI physiology. Although significant advances have been made to develop the drug-delivery systems, most of the dosage forms are still designed on an empirical basis. For oral solid-delivery systems, drug absorption is unsatisfactory and highly variable between the individuals despite excellent in vitro release patterns.[2]

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Published on Web 30/12/2022, www.ijsronline.org

GRDDS can improve controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability. Drugs having narrow absorption window are mostly associated with improved absorption at jejunum and ileum due to their enhanced absorption properties e.g. large surface area, or because of enhanced solubility in stomach as opposed to the more distal parts of the GIT Objective of the Bio/Muco adhesive.[3]

Proposed gastric retentive systems for the enhancement of local drug delivery include floating systems, expandable or swellable systems and bio-adhesive systems. Generally, problems with these formulations are lack of specificity, limited to mucus turnover or failure to persist in the stomach. Gastric mucoadhesive systems are hailed as a promising technology to address this issue, penetrating the mucus layer and prolonging activity at the mucus-epithelial interface.[4]

Helicobacter pylori are one of the most common pathogenic bacterial infections, colonizing an estimated half of all humans. It is associated with the development of serious gastro duodenal disease - including peptic ulcers, gastric lymphoma and acute chronic gastritis. Current recommended regimes are not wholly effective and patient compliance, side-effects and bacterial resistance can be problematic. Drug delivery to the site

of residence in the gastric mucosa may improve efficacy of the current and emerging treatments. Gastric retentive delivery systems potentially allow increased penetration of the mucus layer and therefore increased drug concentration at the site of action.[5]

Antibiotic resistance needs to be taken into account when designing treatment for *Helicobacter pylori* infection. Over the past decade many different therapies were promoted and recommendations changed rapidly. Most doctors lost track, and a great variety of treatments is being used.[6]

Materials and Methods

Materials: All the chemicals and Drugs used in the study were procured from sigma aldrich and all chemicals and reagents used were of analytical grade.

Methods:

Pre-formulation

CHARACTERIZATION OF DRUG:

Physiochemical Properties of Amoxicillin

A) Organoleptic evaluation

It refers to the evaluation by sensory characters-taste, appearance, odor etc.

B) Solubility (at room temp): Solubility is determined in different solvents example – water methanol, 0.1 N HCL, Ethyl Alcohol, and Chloroform.

C) Identification Test

FTIR Spectroscopy: Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound.

The region from 0.8 µ to 2.5 µ is called Near Infra-red and that from 15 µ to 200 µ is called Far infra-red region.

D) Loss on drying: Loss on drying directly measuring by IR moisture balance. Firstly calibrate the instrument by knob then take 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 5 minutes and constant reading set the knob and check % moisture.

E) Determination of pH (1% w/v solution in water): pH was determined by digital pH meter. In this method 1gm of the powder was taken and dissolved in 100ml of distilled water with sonication and filtered, pH of the filtrate was checked with standard glass electrode.

F) Melting point: It is one of the parameters for the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point.

Procedure for determine melting point:

A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

G) Bulk properties: Bulk density is defined as the mass of powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particles become more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease. Bulk properties such as particle size, bulk density etc. of a solid form, are likely to change during process development. Therefore, comprehensive characterization of all preformulation lots is necessary to avoid misleading predictions.

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Procedure: A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml gm/cc, by the formula

H) Compressibility index (Carr's inde)

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material.

I) Hausner ratio:

It indicates the flow properties of the powder and it can be measured by the ratio of tapped density to bulk density.

J) Flow properties

Flow properties determination of powder or granules is the unique tools to avoid the weight variation of tablet. Angle of repose, Carrs index, Hausner ratio are some examples of technique by which we can estimate the flow properties of powder.

K) Angle of Repose

The angle of repose is a relatively simple technique for estimating the flow ability of a powder through a funnel and fall freely onto a surface. The height and diameter of

the resulting cone is measured and using the following equation, the angle of repose can be calculated.

L) MOISTURE CONTENT DETERMINATION

Principle: The titrimetric determination of water is based upon the quantitative reaction of water with an anhydrous solution of sulphur dioxide and iodine in the presence of a buffer that reacts with hydrogen ions.

In the original titrimetric solution, known as Karl Fisher Reagents, the sulfur dioxide and iodine was dissolved in pyridine and methanol. The test specimen may be titrated with the reagent directly, or the analysis may be carried out by a residual titration procedure. The stoichiometry of the reaction is not exact, and the reproducibility of a determination depends upon such factors as the relative concentration of the reagent ingredients, the nature of the inert solvent used to dissolve the test specimen, and the technique used in the particular determination. Therefore, an empirically standardized technique is used in order to achieve the desired accuracy. Precision in the method is governed by the extent to which atmospheric moisture is excluded from the system. The titration of water is usually carried out with the use of anhydrous methanol as the solvent for the test specimen; however other suitable solvents may be used for special or unusual test specimens. (Note: Now-a-days pyridine free KF reagents are coming in which pyridine is replaced by the imidazole, because pyridine has carcinogenic effects).

M) DETERMINATION OF $\lambda_{max.}$

The absorption maxima of Amoxicillin were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Procedure for the determination of $\lambda_{max:}$

Accurately weighed 10 mg of Amoxicillin separately and dissolved in 10 ml of 0.1N HCL in 10 ml of volumetric flask and prepared suitable dilution to make it to a concentration of 10 µg/ml make adequate of sample with concentration range of 10-50 µg/ml Amoxicillin calculate the spectrum of this solution was run in 200-400 nm range in U.V spectrophotometer. (Labindia UV 3000 +)

Preparation of Floating Microsphere of Amoxicillin: Floating microsphere containing Amoxicillin was prepared using emulsion solvent diffusion technique. The drug to polymer ratio used to prepare the different formulations was 1:7. The polymer content was a mixture of Ethyl cellulose Hydroxy propyl mvethylcellulose (HPMC) as shown in table no.5. The drug polymer mixture is dissolved in a mixture of ethanol (8 ml) and dichloromethane (8 ml) was dropped in to 0.75% polyvinyl alcohol solution (200 ml). The solution was stirred with a propeller-type agitator at 40° C temperatures for 1 hour at 300 rpm. The formed floating microspheres were passed through sieve no.12 and washed with water and dried at room temperature in a dessicator. The various batches of floating microsphere were prepared as follows.

Table 1: Formulation

Sr. No	Formulation Code	Amoxicillin (gm)	Sucralfate (gm)	EC (gm)	HPMC (gm)
1	F_1	0.1	0.1	0.7	0.0
2	F_2	0.1	0.1	0.6	0.1
3	F_3	0.1	0.1	0.5	0.2
4	F_4	0.1	0.1	0.4	0.3
5	F_5	0.1	0.1	0.3	0.4
6	F_6	0.1	0.1	0.2	0.5
7	F_7	0.1	0.1	0.1	0.6
8	F_8	0.1	0.1	0.0	0.7

Evaluation of Microspheres

Particle size analysis: Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of floating microspheres were measured by using an optical microscope, and the mean particle size was calculated by measuring nearly 200 particles with the help of a calculated ocular micrometer.

Floating behavior of Floating microsphere:100 mg of the floating microsphere were placed in 0.1 N HCI. The mixture was stirred with paddle at 100rpm. The layer of buoyant microspheres was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microspheres were dried in a desiccator overnight.

Determination of the swelling index: Swelling studies were conducted using the Dissolution Apparatus USP type II (Electro Lab.). No rotation speeds were applied. Pre-weighted floating microspheres 50mg were immersed in 500 mL of the medium (deionized water, DIW; simulated gastric solution, 0.1N HCl) and maintained for 8 h at 37.0 ± 0.5°C. At predetermined

time intervals (0, 0.5, 2, 4, 6, and 8 h), the swollen floating microspheres were removed from the solution, immediately wiped with a paper towel to remove surface droplets, and weighed.

Lag-time and floating time determination of floating microspheres

The floating lag time (FLT) is the time taken for floating microspheres to rise on medium surface, and total floating time (TFT) is the floating duration that floating microspheres remained on surface. To determine the floating lag time, floating microspheres (50mg) were put on 100 ml of 0.1 N HCL in a beaker, and the time is required for a floating microspheres to rise on surface was measured. Then, the duration of each formulation that remained on the surface was determined as total floating.

Drug Entrapment

The various formulations of the floating microspheres were subjected for drug content. 50 mg of floating microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. Again from this solution 2 ml was taken out and add 2 ml of Rhodamine B and Extracted with Chloroform and the absorbance was measured at 558 nm against blank.

Percentage Yield

The prepared microspheres with a size range of 609-874 µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

Shape and Surface Characterization of Floating Microspheres by Scanning Electron Microscopy:

From the formulated batches of floating microspheres, formulations (F_4) which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using scanning electron microscope JEOL, JSM-670F Japan. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 3.0 KV during scanning. Microphotographs were taken on different magnification and higher magnification (500X) was used for surface morphology.

***In-vitro* Release Studies**

The drug release rate from floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples were treated with methyl orange and analyzed spectrophotometrically at 416 nm to determine the concentration of drug present in the dissolution medium.

Drug Release Kinetic Data Analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsmeyer-Peppa's equation (Plotted as Log cumulative percentage of drug released vs Log time).

Results and Discussion:

PHYSICO-CHEMICAL PROPERTIES OF AMOXICILLIN

Organoleptic evaluation

Description

Organoleptic property of Amoxicillin

Table No. 2. Organoleptic property of Amoxicillin

Color	White to almost white crystalline powder
Odor	Odorless
Taste:	Bitter

Solubility

Solubility studies of Amoxicillin have been done in various solvent such as water, Chloroform, Ethanol, Methanol, and 0.1N HCL solution. We were found that a solubility of Amoxicillin is good in a Methanol solution.

Table: 3 Solubility studies of Amoxicillin in different solvent

S. No.	Solvent used	Solubility
1.	Water	Slightly Soluble
2.	0.1 N HCL	Soluble
3.	Ethanol	Slightly Soluble
4.	Methanol	Freely Soluble
5.	0.1N NaOH	Soluble

Melting Point determination: 194-196^{o}C

Loss on Drying (LOD): The percentage of loss on drying of Amoxicillin was found to be 0.87% w/w respectively.

Determination of pH (1% w/v solution in water):

The pH of Amoxicillin was determined by Digital pH meter and found to be 4.9

Identification test by FTIR:

Identification of Amoxicillin by FTIR Spectroscopy with respect to marker compound.

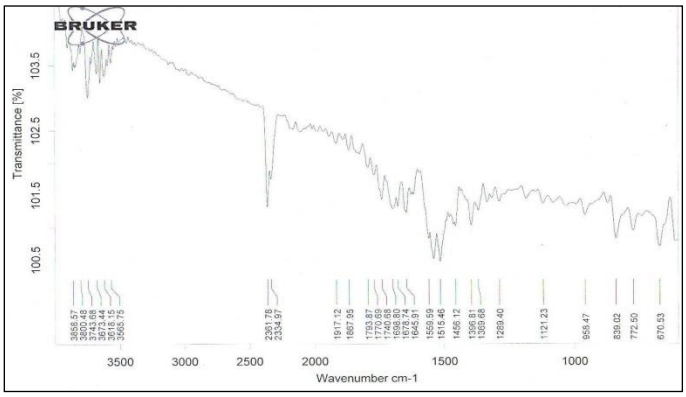

Fig 1:FT-IR Spectrum of Pure Drug (Amoxicillin)

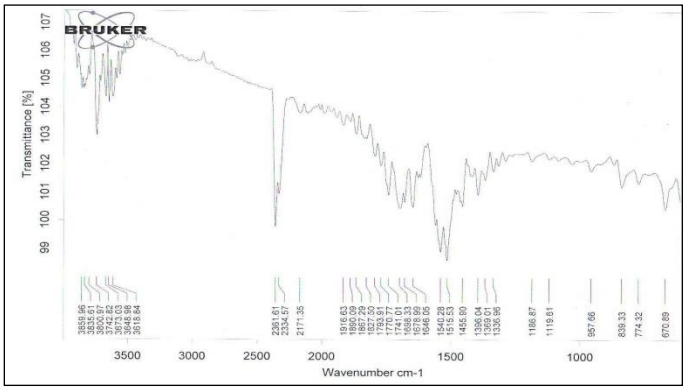

Fig 2: FT-IR Spectrum of Pure Drug (Amoxicillin + All Excipients)

FLOW PROPERTY OF AMOXICILLIN POWDER

Bulk density of powder was found to be 1.1g/cc

Table: 3 Density of formulation

S.No.	Density	Amoxicillin
1	Untapped Density	**0.69g/cc**
2	Tapped Density (after 50 tapping)	**0.86g/cc**

Compressibility Index (%): The compressibility index of Amoxicillin was found to be 19.77%.

Hausner ratio: The Hausner ratio of Amoxicillin was found to be 1.24**.**

Angle of Repose: The Angle of repose of Amoxicillin is 40.57 degree.

Particle size: pass through 40# is 100 (%w/w).

Moisture by Karl-Fischer Apparatus (KF): 0.81%

λ_{max} by Uv Spectroscopy: The λ_{max} found for Amoxicillin is 238.0 nm as shown in Figure.

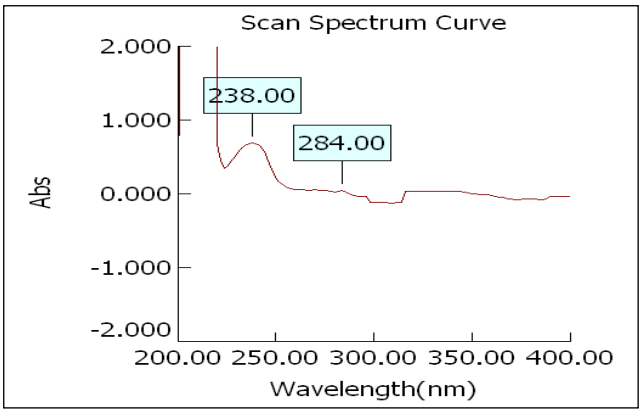

Fig 4: Determination of λ_{max} of Amoxicillin

Table: 4 Calibration curve of Amoxicillin

Replicate	10	20	30	40	50
1	0.145	0.285	0.418	0.561	0.702
2	0.143	0.283	0.419	0.562	0.703
3	0.145	0.286	0.418	0.561	0.702
Mean	0.144	0.285	0.418	0.561	0.702
S.D.	0.001	0.002	0.001	0.001	0.001
% RSD	0.800	0.537	0.138	0.103	0.082

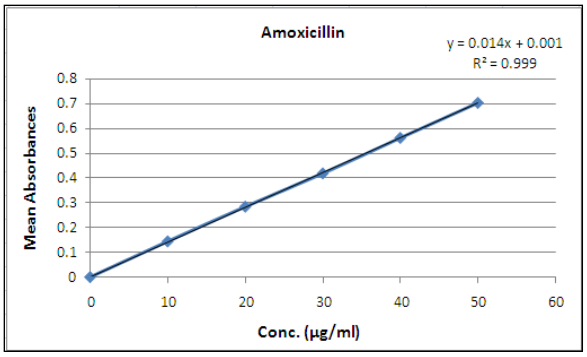

Fig 3: Calibration curve of Amoxicillin

Particle size analysis:

Table 5: Mean particle size of Different Batches of Amoxicillin microsphere

S. No	Formulation code	Mean particle size (µm)
1.	F_1	212±12
2.	F_2	225±21
3.	F_3	264±23
4.	F_4	236±25
5.	F_5	242± 24
6.	F_6	244±40
7.	F_7	210±23

Floating behavior of microsphere

Amoxicillin Microsphere was dispersed in 0.1N HCl as simulate gastric fluid. Floating ability of different formulation was found to be differed according to EC and HPMC ratio. F_1-F_4 formulations showed best floating ability (91.47-72.97%) in 6 hours. F_5-F_8 formulation showed less floating ability (66.12-45.09%) as showed in Table-6. The floating ability of microsphere is decreased by increasing the HPMC ratio

Table 6: Floating behavior of microsphere (PERCENTAGE BUOYANCY FOR DIFFERENT FORMULATION)

Formulation	1 hour	2 hours	4 hours	6 hours
F_1	98.41	97.08	93.23	91.47
F_2	98.11	95.58	92.17	87.34
F_3	98.54	95.64	85.34	78.45
F_4	99.54	92.49	80.57	72.97
F_5	98.72	91.95	73.49	66.12
F_6	98.45	86.62	65.14	57.76
F_7	88.34	75.41	56.04	45.09

Determination of the swelling index and Lag-time and floating time determination of floating microspheres:

Table shows the results of the floating time of seven prepared formulations over 12 hours. The investigated gastric floating systems employed sodium bicarbonate (NaHCO3) as a gas-forming agent, which is trapped in a hydrogel matrix (HPMC and EC).The *in vitro* study revealed that most formulations are able to keep the drug buoyant for more than 12 h. This suggests that the gel layers enabled efficient entrapment of the generated CO_2 bubbles. The floating lag time for most formulations was below 12 minutes, regardless of the content of polymers used, indicating significance of the polymers concentrations. The interaction between sodium bicarbonate ($NaHCO_3$) as a gas-generating agent and the dissolution medium (0.1 Mol L−1 HCl, pH 1.3) generated and entrapped CO_2 inside the jellified polymeric matrices, inducing the microspheres to float. A decrease microspheres-specific gravity causes the microspheres to float on extended residence time in the stomach, improving absorption.

Table 7: swelling index and Lag-time and floating time of floating microspheres:

Formulation	% Swelling Index	Floating lag time (m)	Total floating time (h)
F_1	37.68	12	12
F_2	33.38	3	10
F_3	35.62	8	8
F_4	38.23	10	12
F_5	37.90	4	10
F_6	34.20	4	8
F_7	35.60	10	12

Drug Entrapment:

The drug entrapment efficacies of different formulations were in range of 48.47 - 74.19 % w/w as shown in Table No-7.8. Drug entrapment efficacy slightly decrease with increase HPMC content and decreased EC ratio in Microspheres. This is due to the permeation characteristics of HPMC that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of Amoxicillin microspheres.

Table 8: Drug Entrapment For Different Formulation

Formulation	Drug entrapment (% w/w)
F_1	76.19
F_2	70.59
F_3	66.23
F_4	64.76
F_5	61.01
F_6	57.38
F_7	48.47

Percentage Yield:

Percentage yield of different formulation was determined by weighing the Microspheres after drying. The percentage yield of different formulation was in range of 56.84 - 82.87%

Table 9: Percentage yield of different formulation

Formulation	Percent Yield (%)
F_1	82.87
F_2	78.53
F_3	76.47
F_4	71.56
F_5	69.31
F_6	66.03
F_7	56.84

Scanning Electronic Microscopy:

Shape and surface characteristic of Amoxicillin microspheres examine by Scanning Electronic Microscopy analysis. Surface morphology of formulation examines at different magnification, which illustrate the smooth surface of floating Microspheres.

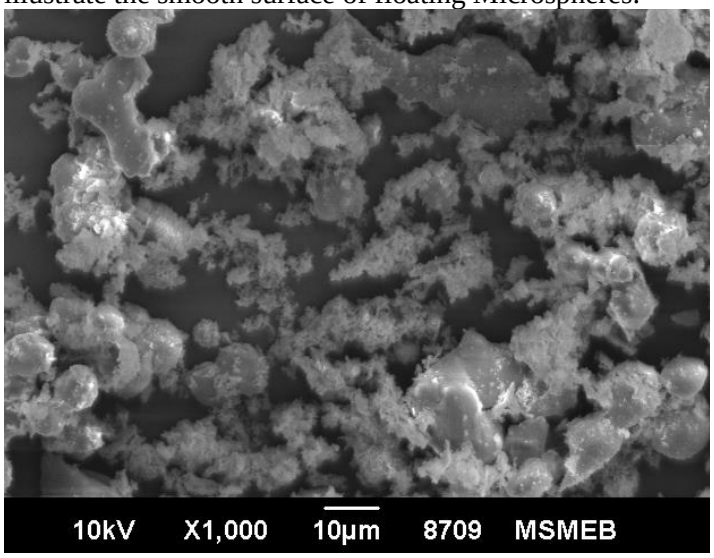

Fig 5: Scanning Electronic Microscopy Image of Optimized Formulation F-7

***IN-VITRO* Drug release study: *In vitro* drug release study of Amoxicillin loaded Floating Microsphere**

Table No 10: Comparative Release study of Formulation F-1 to F-7

Time	% of Drug Release						
(hr)	F1	F2	F3	F4	F5	F6	F7
0.5	16.429	15.000	14.286	14.286	17.857	16.429	14.286
1.0	26.536	18.607	18.571	18.571	28.036	25.821	22.857
1.5	30.679	27.357	27.321	27.321	34.393	31.357	33.964
2.0	57.107	32.929	32.893	32.893	43.857	43.536	39.143
3.0	71.214	60.143	40.821	40.821	61.571	54.821	58.786
4.0	81.607	77.214	52.643	52.643	71.500	78.000	56.464
6.0	95.214	85.714	72.107	72.107	78.214	93.643	66.036
8.0	100.036	90.179	86.714	86.714	95.107	99.893	95.250

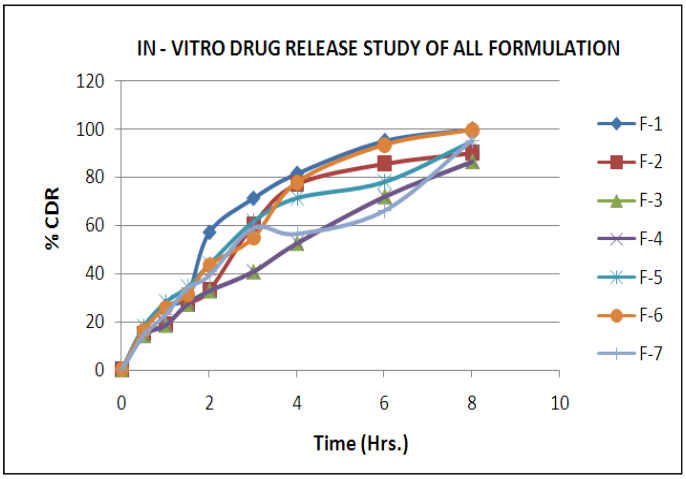

Fig 6: Graph of release study of formulation F1-F7

Table 11: Release Kinetics of Optimized Formulation F-7

Time (Hrs.)	% CDR	Log T	Root T	Log % cum. drug remain to be release	Log cum. % drug release
0.5	14.286	-0.301	0.707	1.933	85.714
1	22.857	0.000	1.000	1.887	77.143
1.5	33.964	0.176	1.225	1.820	66.036
2	39.143	0.301	1.414	1.784	60.857
3	58.786	0.477	1.732	1.615	41.214
4	56.464	0.602	2.000	1.639	43.536
6	66.036	0.778	2.449	1.531	33.964
8	95.25	0.903	2.828	0.677	4.75

Fig 7: Graph of Zero order release kinetics of F-7

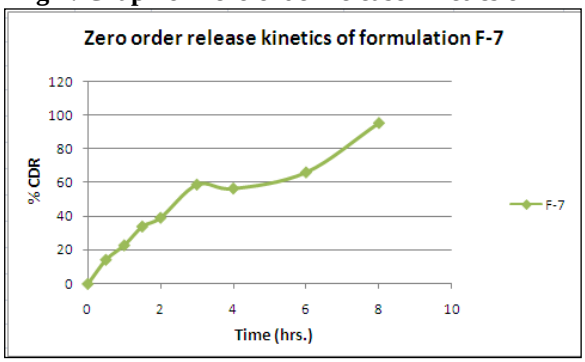

Fig 8: Graph of First order release kinetics of F-7

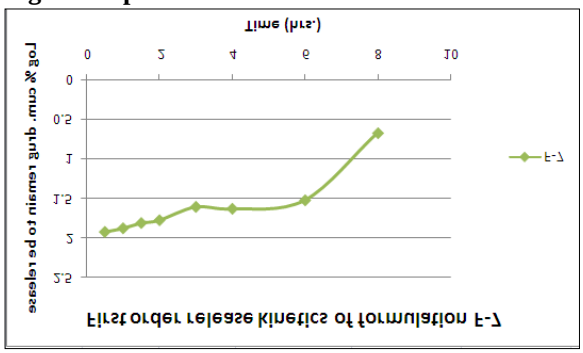

Fig 9: Graph of Higuchi release Kinetics

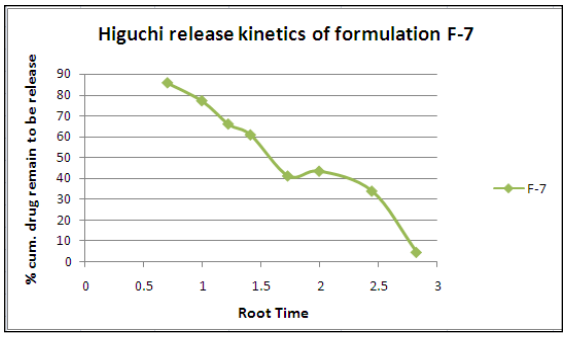

Fig 10: Graph of Korsemayer – Papas Kinetics

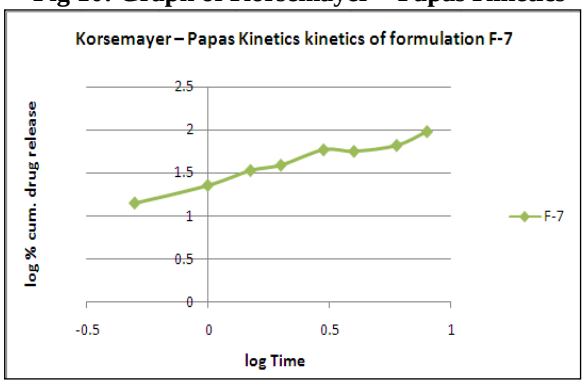

Table 12:. Comparative study of regression coefficient for selection of optimize Formulation F-7

Zero order		First order	Higuchi	Korsmayer
r2	0.931	0.831	0.954	0.972

Conclusion: Drug absorption in the gastrointestinal tract is a highly variable process. Floating microspheres are promises to be a potential approach for gastric retention enhances the bioavailability and controlled delivery of various therapeutic agents. Significant attempts have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance.

Floating microspheres as gastro retentive dosage forms precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

In-vitro data obtained for floating microspheres of Amoxicillin showed good incorporation efficiency, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. From the results it can be concluded that the drug release from the floating microspheres controlled by the polymer proportion. Prepared formulation showed best appropriate balance between buoyancy and drug release rate.

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