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Formulation, Development and Characterization of Mucoadhesive Microspheres for Delivery of Amoxicillin and Rabeprazole Sodium for the Treatment of Gastric Ulcer

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Abstract: Microspheres contain a critical bit of novel medicine movement system by standards of their little size and capable carrier limit. It is recommended that the drifting empty microcapsules would be an interesting gastro retentive controlled delivery conveyance framework for drugs. In this study, an endeavor was made to utilize carbopol-934, sodium carboxymethyl cellulose (SCMC), sodium alginate and fluid paraffin as a mucoadhesive polymer to set up the mucoadhesive microsphere that clings to the gastric mucosa, to expand the medication's gastric home time and to deliver the medication in a controlled delivery way.

Keywords: Amoxicillin, Drug Delivery, Gastric Ulcer, *Helicobacter pylori*, Microsphere, Mucoadhesive system, Rabeprazole

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Introduction

Peptic ulcer is an acid-induced lesion of the digestive tract typically located in the stomach or proximal duodenum and characterized by a loss of denuded mucosa that spreads to the sub-mucosa or muscularis propria. In the general population, the overall prevalence of peptic ulcer disease is 5-10%, but new epidemiological studies have shown a decrease in incidence, hospital admission rates, and mortality due to peptic ulcer (Lanas *et al.*, 2018). This is most likely secondary to the emergence of new therapies and improved hygiene, culminating in a decline of *Helicobacter pylori* (*H. pylori*) infections. *H. pylori* colonises approximately 50 per cent of the total population, and is perhaps the most commonly accepted cause for peptic ulcer illness. *H. pylori* is more prevalent

in agricultural nations, particularly in Africa, Central America, Central Asia, and Eastern Europe (Hooi, 2017). The medication organization's oral course provides the most beneficial and preferred approaches for drug conveyance of simple body flow. In either case, oral organization in customary measuring frameworks of the vast majority of drugs has temporary constraints attributable to their powerlessness to limit and confine the gastro-intestinal lot system. Microspheres are the drug conveyance system linked to the transporter through which the molecule size goes from a distance of 1-1000 µm through a medication core and external polymer layers as a covering material.

As a drug carrier, microspheres are one such technique that can be used in an assisted managed delivery design. Microspheres are microscopic spherical particles with sizes in the range of micrometers (1 µm to 1000 µm on a daily basis). Microspheres are referred to a semi crop particle at times (Chaturvedi and Sah, 2009).

Microspheres can possibly be used as spatial drug conveyance for controlled medication. The combination of mucoadhesives with microspheres facilitates efficient drug absorption and increased bioavailability. By using homing gadgets (legend) such as plant lectin, bacterial bond etc. on the exterior of the microspheres, explicit focusing of drug to the retention site is done. Mucoadhesive microspheres may be modified to stay tight to gastrointestinal tract (GIT) mucosal linings, thereby giving the likely effects of minimal as well as simple drug consumption in a regulated manner (Gabor *et al.*, 1997; Haas *et al.,* 2002).

The aim of the current investigation was to build up and break down the mucoadhesive microspheres of Amoxicillin and Rabeprazole by incorporating the potential advantages of mucoadhesion with directed medication which convey an utilizing diverse polymer proportions to give the medication a supported delivery component for broadened gastrointestinal ingestion. Semi-formulated broad-spectrum anti-infective such as ampicillin results in high serum levels when administered orally but it is resistant to corrosive gastric acid. Clavulanic corrosive (a beta lactamase inhibitor) is generally utilized for amoxicillin since it is inclined to debasement of beta-lacatamase. In the group of proton siphon inhibitors, rabeprazole is an enemy of ulcer drug. It is a pro-drug - it changes into dynamic sulphenamide type in the corrosive climate of the parietal cells. Rabeprazole represses gastric cell covering H^+, K^+ATPase and portion subordinate stifles the emission of basal and actuated gastric corrosive.

To determine the entirety of the above results and to limit the dosing recurrence of the medicine, a fresher and better plan should be made that conveys the medication to the body for a full and expanded period. Consequently, it would be clearly helpful to improve controlled delivery measurements plans of Rosiglita zone maleate to deliver the medication consistently over an all-inclusive time of activity, for example in constant delivery habits.

The ingestion site of rosiglitazone maleate is most normally situated in the digestive tract. Dose definitions that are put away in the stomach can build assimilation, help drug quality, and lessening dosing necessities. In the plan and creation of the cutting edge drug conveyance framework, measurements details that can dependably screen the delivery time and target medication to a specific body area have had a colossal effect. Mucoadhesive microspheres are a fundamental component of a particularly present day strategy for drug conveyance. Sodium carboxy methyl cellulose (SCMC), carbopol-934 and sodium alginate are the polymers which show great mucoadhesive properties, capture productivity and release the medication in supported delivery way. In this investigation, an endeavor was made to set up the mucoadhesive microsphere that clings to the gastric mucosa, and to deliver the medication in a controlled delivery way.

Materials and Methods

All chemical substances consisting starter

materials, reagents and solvents were purchased from the Merck and Sigma-Aldrich. Melting point of the synthesized compounds was done by Theile tube capillary method.

Optimized Method for Preparation of Microspheres:

Amoxicillin and Rabeprazole stacked mucoadhesive microspheres were set up by w/o emulsification dissolvable vanishing strategy utilizing three distinctive mucoadhesive polymers, viz. Carbopol 934, HPMC and Sodium CMC (Kawashima *et al*., 1992; Saffari *et al*., 2008).

Preparation of Amoxicillin and Rabeprazole Microsphere:

Emulsification-Solvent Evaporation:

Precisely weighted measure of the Carbopol, HPMC and Sodium CMC polymers as depicted in Table 1 were broken down into 50.0 ml of Acetone to form a homogeneous polymer system. Amoxicillin and Rabeprazole was then scattered in it and blended completely. At 150°C, this drug-containing natural stage was steadily vacuumed into fluid paraffin (50 ml) containing 1% (w/w) of Span-80 with blending at 1000 rpm to create a uniform emulsion. From that point, it was allowed to reach room temperature and mixing was carried out until dissipated and smooth-walled, inflexible and discrete microspheres were created by leftover acetone $(CH_3)_2CO$. Through decantation, the microspheres were extracted and the stock was washed with petroleum ether-hexane and dried for 3 h at room temperature. The microspheres were then mounted over inter woven calcium chloride in desiccator. (Mehat, 2002; and Nagasamy Venkatesh *et al*., 2009).

Characterization of Microspheres:

Particle Size Determination:

The particle size distribution for the microspheres was measured using a series of normal sieves using an analysis of the sieving method. Particles of a variety of sizes ranging from 50 to 1500 µm are determined by the sieving process. This approach explicitly provides weight distribution. A beneficial use of tablets and spheres in the growth of dosage form is the sieving process (Aulton, 2002; Swamy *et al.*, 2007).

Encapsulation Efficiency and Drug Loading:

A weighted volume (50 mg) of microspheres was suspended in 50 ml of ethanol for 15 min to assess the medication quantity encapsulated in the microspheres in order to thoroughly isolate the trapped drug. Through Whatman filter paper, the solution was filtered. 1 ml of the solvent was separated and reduced to 50 ml with a phosphate buffer solution of pH 7.4. This solution was examined at 247 nm with a UV spectrophotometer for the drug material. We get the percentage content of medications by multiplying this concentration with the dilution factor (Streubel *et al*., 2003; Jayvadanpatel *et al*., 2005).

EE (%)=Actual Drug Content /Theoretical Drug ContentX100

DL (%) =Actual Drug Content/Weight of Powdered Microspheres X 100

Degree of Swelling and Per cent Mucoadhesion:

In order to assess the percentage moisture content that shares an idea of its hydrophilic existence, the Amoxicillin and Rabeprazole filled microspheres were analysed. The microspheres were initially weighted (w1) and retained for 24 h in desiccators containing calcium chloride at 37°C. The final weight (w2) was observed as there was no further change in the weight of the sample (Swamy *et al*., 2007).

$$\text{Moisture Percentage} = w1-w2/w2\times100$$

Scanning Electron Microscopy (*SEM*):

To observe the microspheres, a scanning electron microscopy was used. They were mounted directly on the SEM sample stub using double-sided sticking tape and coated with gold film with an ion spillter with a 3 nm (30 KV HV mode), 10 nm (30 KV HV mode) and 40 nm (30 LV mode) resolution gold aim and fitted with a vacuum system.(Swamy *et al*., 2007)

In vitro Mucoadhesion Studies:

Using a falling fluid film process, *in vitro*

Table 1: Formulation design of Amoxicillin and Rabeprazole mucoadhesive microspheres using different polymer concentrations

S. No.	Ingredients	Formulation code							
		MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8
1	Amoxicillin (mg)	500	500	500	500	500	500	500	500
	Rabeprazole (mg)	20	20	20	20	20	20	20	20
2	Sodium CMC (mg)	400	-	400	-	400	-	400	-
3	Sodium alginate	-	200	-	200	-	200	-	200
4	Carbopol 934 (mg)	100	200	100	200	100	200	100	200
5	Liquid Paraffin (ml)	25	50	25	50	25	50	25	50
6	Span 80 (ml)	1	2	3	1	2	3	3	3
7	Acetone (ml)	50	50	50	50	50	50	50	50

microsphere mucoadhesion studies were investigated. A little bit of the sheep's intestinal mucosa was mounted on a glass slide and specifically gauged microspheres were sprayed on the mucosa. In order to allow the polymer to comply with the film that was ultimately Put in the cell at a point of 45º linked to the external array, this glass slide was retained for 15 min in a dessicator. Phosphate support arrangement pH 6.4, warmed to 37 ± 5 ℃, was distributed on the microspheres and layers everywhere at a rate of 1 ml/min. Washings were collected at different time spans and microspheres were collected by centrifugation accompanied by drying at 50 ℃ (Dandagi *et al.*, 2007). The weight of washed out microspheres was calculated and the following formula was used to quantify per cent mucoadhesion:

$$\% \text{ Mucoadhesion} = (W_a - W_b) \times 100/Wa$$

Where, Wa=weight of microspheres applied; Wb=weight of microspheres leached out.

In vitro Dissolution Study:

An *in vitro* dissolution profile of each formulation was calculated using the USP XXIII spinning basket process (900 ml pH 6.8- phosphate buffer, 100 rpm and 37±0.5^{0}C). Microspheres equal to 100 mg of Amoxicillin and Rabeprazole filled the basket of the dissolution apparatus. Dissolution study for 12 h. 1 ml of the sample was removed from the dissolution medium at acceptable time intervals and diluted to10 ml separately with 0.1 N HCl (pH 1.2) and pH 7.4 phosphate buffer and replaced with a fresh buffer for the same amount. Using the Shimadzu 1700 UV spectrophotometer at 247 nm, absorption was measured. (Matiholimath *et al.*, 2007).

FTIR Spectroscopy:

The FTIR spectral analysis was carried out by pressed pellet technique. IR spectrum of any substance gives information about the group present in a specific substance. An IR spectrum of drug was taken using (KBr potassium bromide) pellets. Small quantities of drug sample were mixed with oil, and a drop was placed between KBr pellets and spread uniformly. The pellets were placed in the holder, and an infrared spectrum was taken. The range of scanning was 400-4000 cm^{-1}. Different peaks in the infrared spectrum were interpreted for presence of various groups in the structure of the drug. The observed IR spectra of

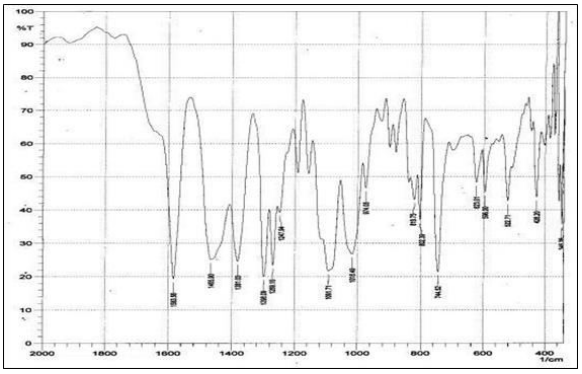

Fig. 1: IR Spectra of Amoxicillin.

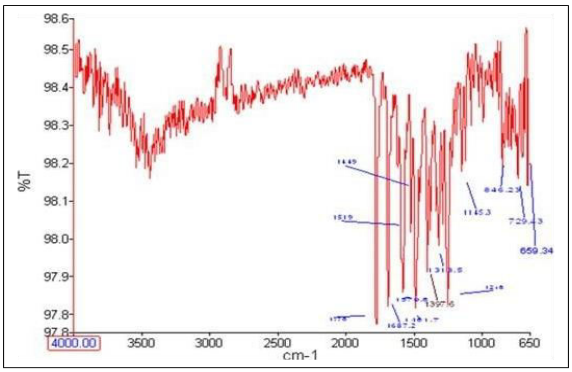

Fig. 2: IR Spectra of Amoxicillin.

the drug are shown in Figures 1 and 2.

Stability Studies:

Stability tests must be conducted in order to determine the degree of degradation and to ensure that corrosion has not reached an acceptable level of patient safety and product activity. The six clumps of microspheres stacked with Amoxicillin and Rabeprazole, Plan F1, F2 and F3 were tested for reliability testing. All the specifics were grouped into three sets of examples and put at (i) 4±1^{0}C and 60±5% RH; (ii) 37±2 ^{0}C and 65 ± 5% RH. The drug distribution and per cent epitome of chosen plans are resolved after 30 days (ICH–Technical Coordination, 2008).

Results and Discussion

Formulation of Mucoadhesive Microsphere:

The formula for formulation of Mucoadhesive Microsphere (Fig. 3) by Emulsification-solvent evaporation and their results are shown in Table 2. The particles were observed to be smaller than the micron scale in this technique, the structure was circular, and no aggregation took place.

Percentage yield and Particle Size of prepared Mucoadhesive Microspheres:

The rate yield of microspheres was determined by utilizing the heaviness of end result in the wake of drying concerning complete weight. The most extreme rate yield was found of MF4 bunch and was noted to be 91.46% among all the groups. The creation yields of microspheres were discovered to be between 82.71% to 91.46% as illustrated in Table 2 and Figure 6.

The normal molecule size of Amoxicillin and Rabeprazole microspheres were gone from 296.43 µm - 377.08 µm. The mean molecule size was altogether increments with expanding mucoadhesive polymer fixation which might be credited to high thickness of mucoadhesive polymer arrangement (Fig. 7).

Per cent Encapsulation Efficiency and Per cent Drug Loading:

Per cent Encapsulation Efficiency and Per cent Drug loading of the formulations were carried out and were found to be within the range between 81.66 to 93.11% and 18.21 to 22.76%, respectively (Table 3, Figs. 8, 9).

Degree of swelling and Percent mucoadhesion:

Degree of swelling and percentage mucoadhesion of the formulations were carried out and were found to be within the range between1.13to1.73 and 83.6to96.2%, respectively (Table 4, Figs. 10, 11).

Scanning Electron Microscopy:

The outer surface of the MF4 formulation (Fig. 3) was smooth and dense, while the inner surface was porous, as evidenced by scanning electron microscopy (Fig. 4). The shell of microspheres also revealed some porous structure that could be caused by solvent evaporation stuck in the shell of

Fig. 3: Prepared Amoxicillin and Rabeprazole loaded mucoadhesive microspheres (MF4).

Table 2 : Physicochemical Properties of Amoxicillin and Rabeprazole Mucoadhesive Microspheres

S. No.	Formulation code	Percentage yield	Average particle size
1	**MF1**	85.26± 1.44	345.71±5.899
2	**MF2**	90.64± 1.36	330.45±4.936
3	**MF3**	83.41± 1.24	356.00±5.587
4	**MF4**	91.46± 1.54	377.08±8.175
5	**MF5**	82.71± 1.56	315.14±7.553
6	**MF6**	86.12±1.72	296.43±9.305
7	**MF7**	88.19± 1.72	303.47±6.305
8	**MF8**	87.62± 1.72	322.13±7.305

microspheres after forming a smooth and dense coating.

In vitro dissolution study:

In vitro release tests of prepared mucoadhesive microspheres Amoxicillin and Rabeprazole Mucoadhesive microspheres were conducted as a diffusion medium at pH 1.2 buffer for a duration of 12 h. A biphasic release with an initial burst effect was seen in the release. 19.6, 16.48, 16.55, 16.12, 17.74, 15.59, 16.74 and 14.59 for MF 1 to MF 8, respectively were released at the end of the first 30 min drug release (Fig. 5). The burst release process may be due to the medication loaded on the microspheres or incomplete drug entrapment. The total per centre lease was observed to be 94.5, 85.00, 88.08, 96.27, 84.04, 81.35, 86.04 and 83.35 at the end of the 12th h for MF1, MF2, MF3, MF4, MF5, MF6, MF7 and MF8, respectively.

The R2 values (Table 6) for zero order kinetics were 0.976, 0.905, 0.934, 0.986 for MF1, MF2, MF3, MF4, MF5, MF6, MF7 and MF8, respectively,

Table 3: Per cent drug loading and per cent encapsulation efficiency of prepared formulations

S. No.	Formulation code	Abs at 247nm	Theoretical content (mg)	Actual content (mg)	% Drug Loading	%Encapsulation Efficiency
1	MF1	0.096	520	483.72	21.28	91.86
2	MF2	0.091	520	506.71	18.21	83.35
3	MF3	0.095	520	480.131	20.79	90.06
4	MF4	0.086	520	509.22	22.76	93.11
5	MF5	0.089	520	476.675	19.29	86.26
6	MF6	0.083	520	499.32	20.16	81.66
7	MF7	0.081	520	498.05	21.00	91.04
8	MF8	0.088	520	503.7	20.67	89.05

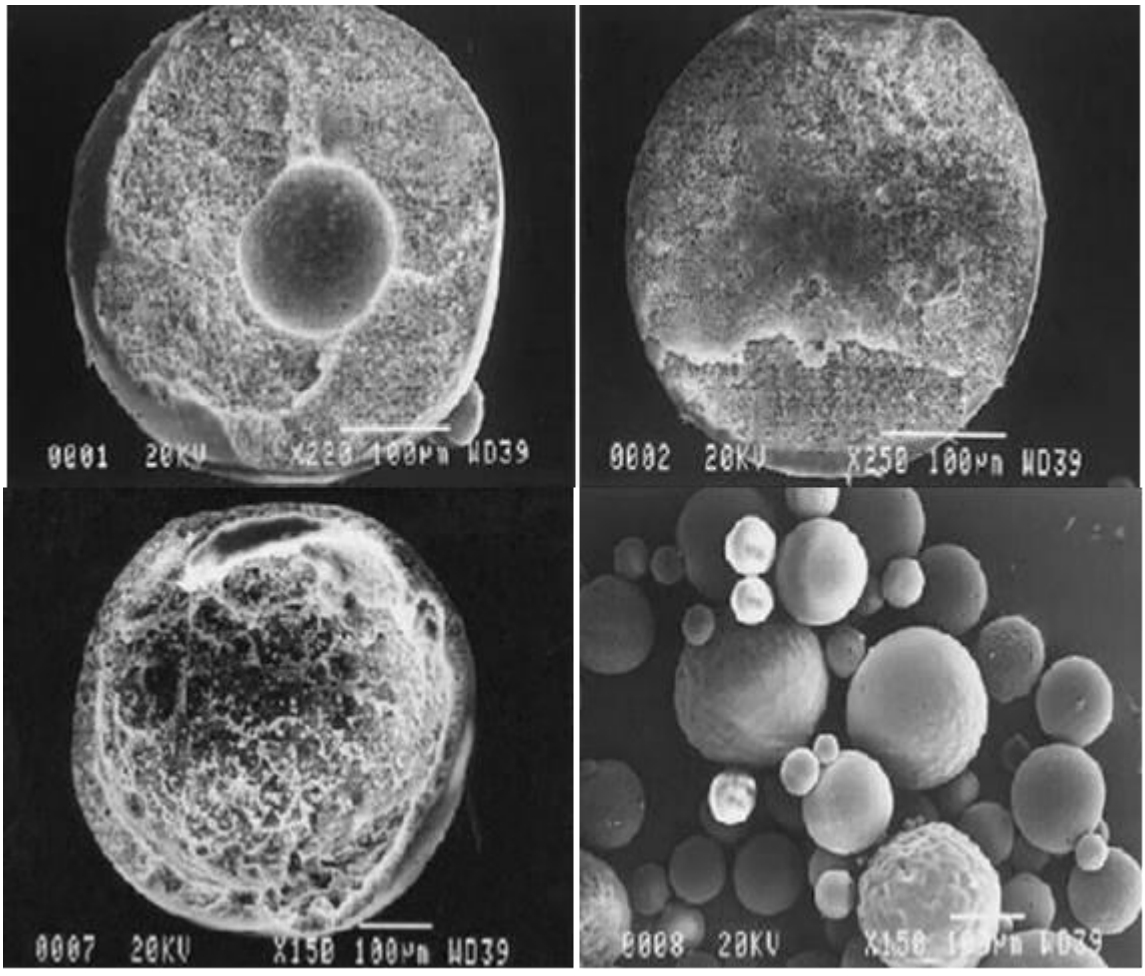

Fig. 4: SEM Photograph of Amoxicillin and rabeprazole loaded Microspheres (MF4).

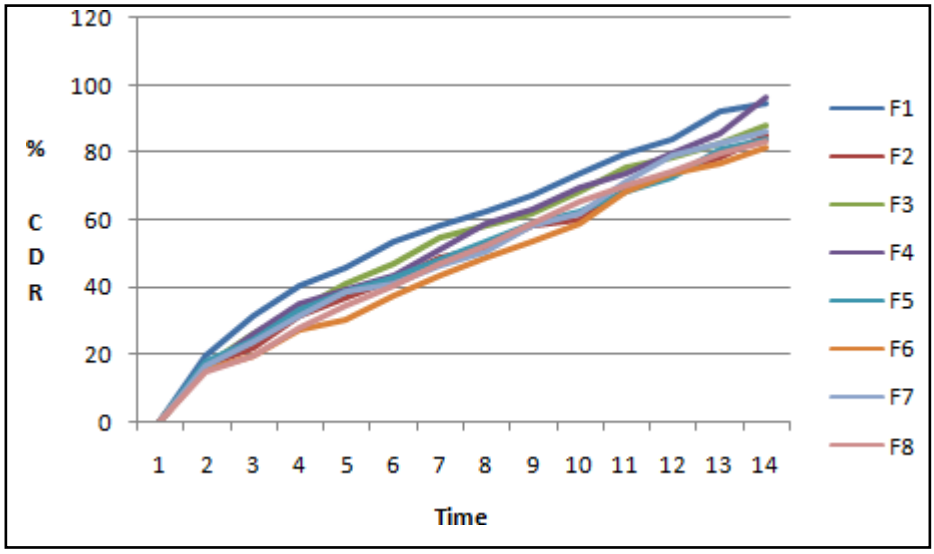

Fig. 5: Comparative in vitro release profiles of amoxicillin and rabeprazole microspheres in 0.1NHCl pH 1.2.

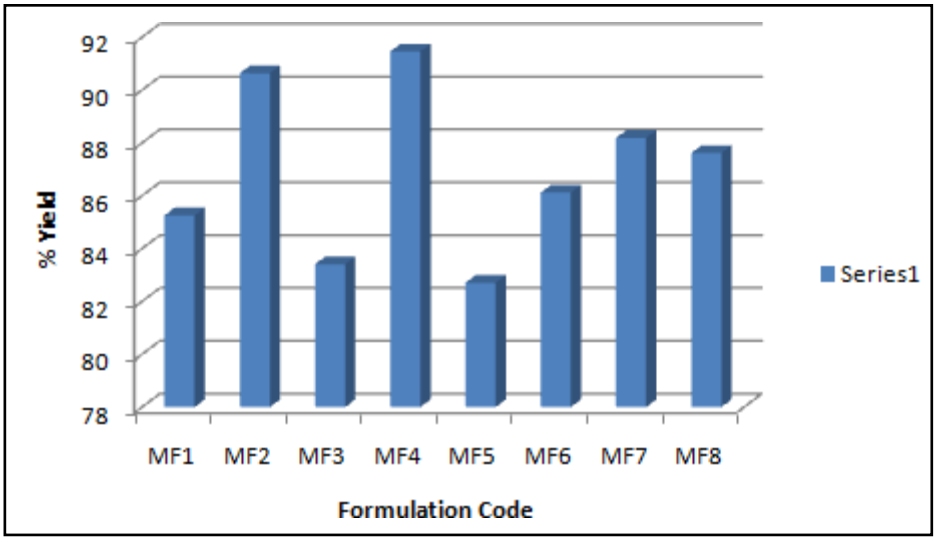

Fig. 6: Percentage yield of Amoxicillin and Rabeprazole Mucoadhesive Microspheres.

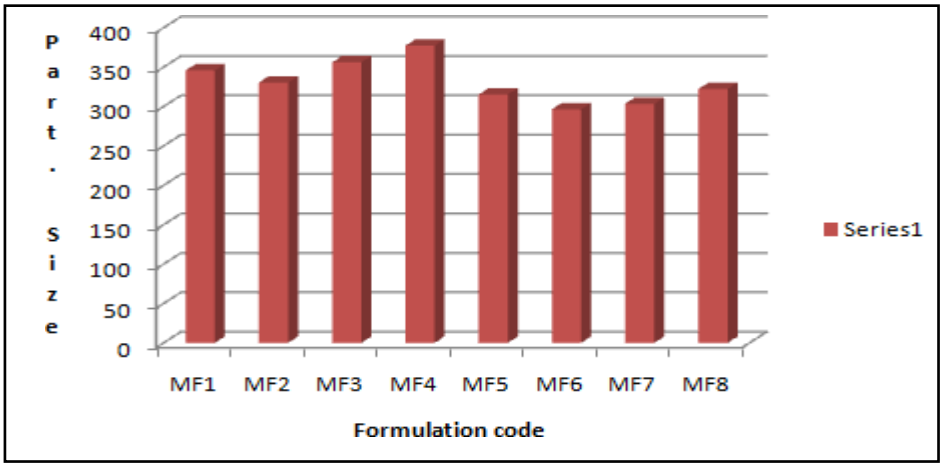

Fig. 7: Average particle size of Amoxicillin and Rabeprazole Mucoadhesive Microspheres.

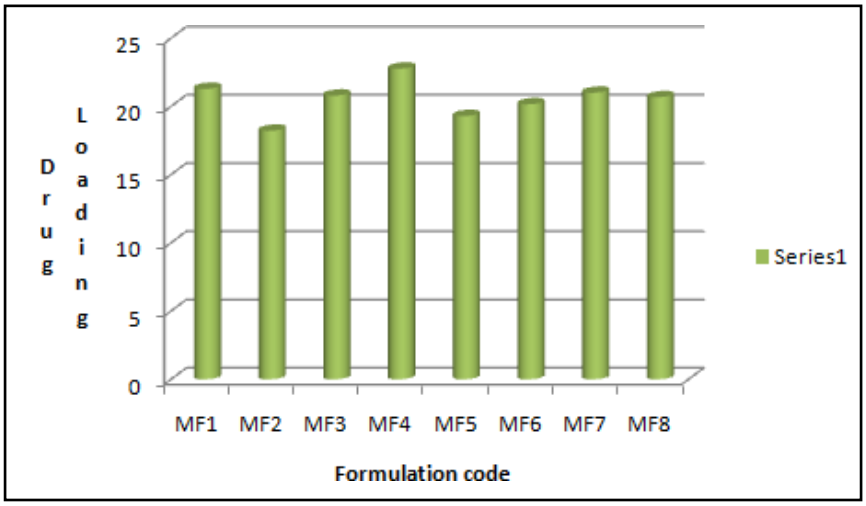

Fig. 8: Per cent drug loading of Formulation.

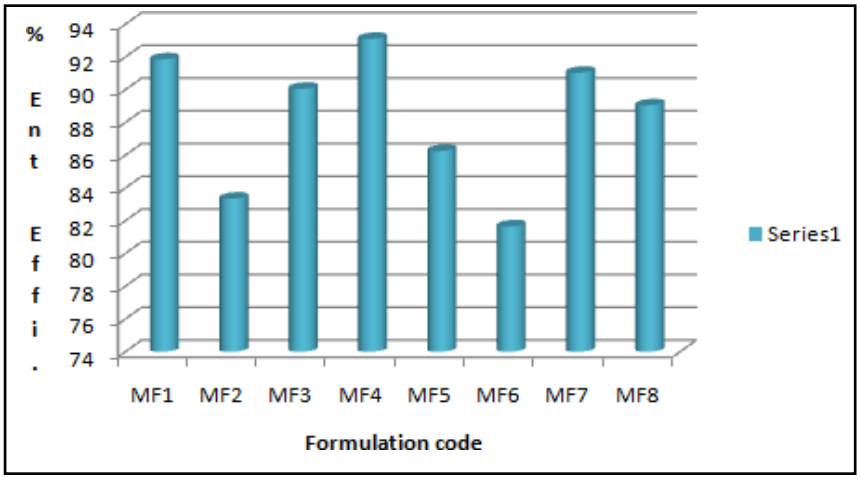

Fig. 9: Per cent Entrapment Efficiency of Formulation.

Table 4 : Degree of swelling and per cent Mucoadhesion

S. No.	Formulation code	Degree of swelling	% Mucoadhesion
1	**MF1**	1.73	95.5
2	**MF2**	1.29	88.3
3	**MF3**	1.59	85.7
4	**MF4**	1.17	96.2
5	**MF5**	1.53	93.1
6	**MF6**	1.13	83.6
7	**MF7**	1.65	88.6
8	**MF8**	1.63	90.5

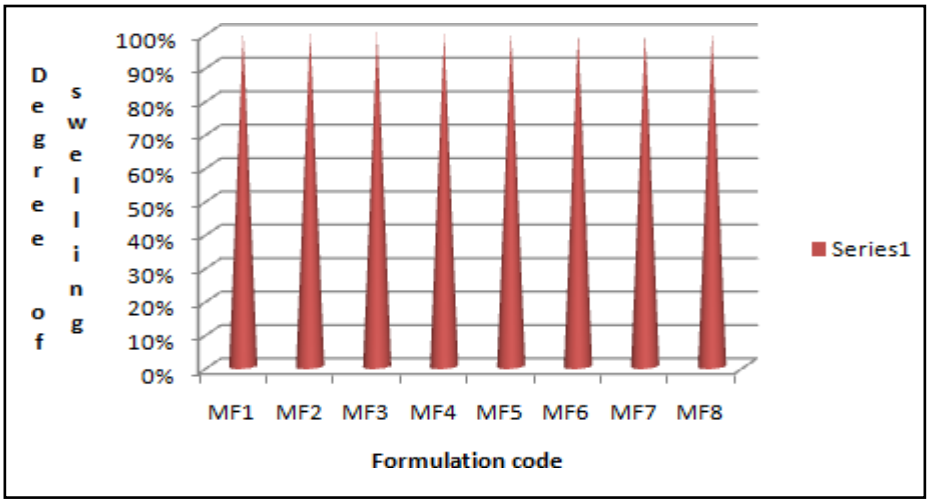

Fig. 10: Degree of swelling of Amoxicillin and Rabeprazolelo added microspheres.

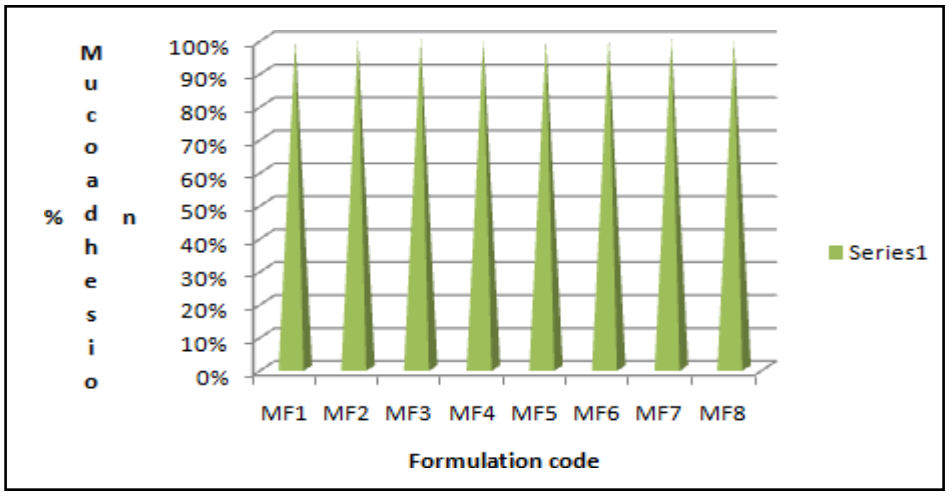

Fig. 11: Percentage mucoadhesion of Amoxicillin and Rabeprazolelo added microspheres.

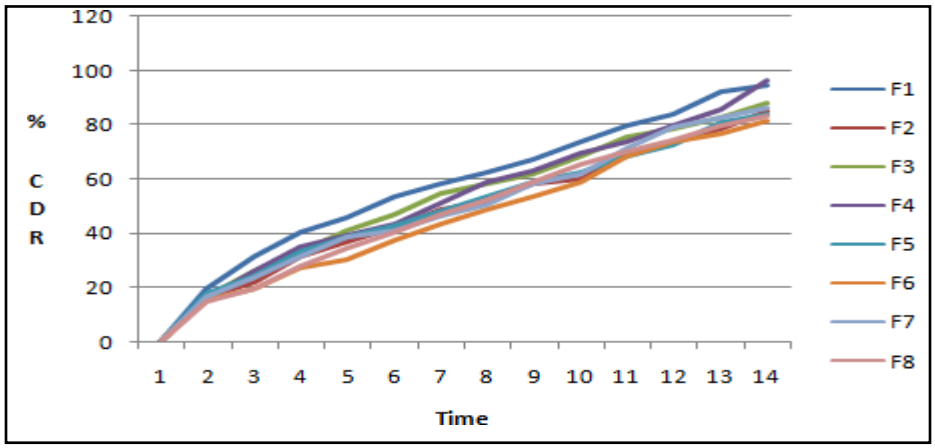

Fig. 12: Comparative in vitro release profiles of Amoxicillin and Rabeprazole microspheres in 0.1N HCl, pH 1.2.

Table 5: In vitro release of Amoxicillin and Rabeprazole microspheres in 0.1N HCl, pH 1.2

Time (h)	%Cumulative drug release							
	MF1	**MF2**	**MF3**	**MF4**	**MF5**	**MF6**	**MF7**	**MF8**
0	0	0	0	0	0	0	0	0
0.5	19.6	16.48	16.55	16.12	17.74	15.59	16.74	14.59
1	31.44	22.23	25.90	25.87	24.64	19.69	23.64	19.69
2	40.12	31.24	33.49	34.97	33.31	27.24	31.31	28.24
3	45.93	37.13	41.22	39.21	38.73	30.28	38.73	34.28
4	53.44	42.37	47.13	43.60	43.02	37.20	41.02	40.20
5	58.29	48.58	54.92	51.28	48.08	43.33	46.08	47.33
6	62.57	51.86	58.29	58.56	53.36	48.44	50.36	52.44
7	67.08	57.99	62.03	63.23	59.27	53.67	58.27	58.67
8	73.48	60.24	68.61	69.41	62.46	58.55	61.46	65.55
9	79.91	68.89	75.79	73.80	68.28	68.04	71.28	70.04
10	83.55	73.61	78.33	79.68	72.66	73.69	78.66	74.69
11	91.87	78.67	82.46	85.38	81.25	76.64	82.25	79.64
12	94.5	85.00	88.08	96.27	84.04	81.35	86.04	83.35

suggesting that the drug followed zero order release. The Higuchi model was exposed to *in vitro* data to figure out the drug release process. Linear were the Higuchi plots with all the formulations. It confirms release following the process of diffusion of Higuchi (Table 5 and Fig. 12). The formulations were subjected to Peppas plots, the effects were rather linear and the slope value (n value) was determined to mean that the compound was released by the Ficki an diffusion process with in a defined limit.

Stability studies:

The stability tests of the prepared microspheres of Amoxicillin and Rabeprazole were carried out by storing the MF4 formulations for one month at 4 ± 1°C and 60±5 per cent RH and 37 ± 2 °C and 65 ± 5 per cent RH. Two parameters were carried out, namely the drug substance percentage and *in vitro* release trials as illustrated in Table 7.

Conclusion

The outcomes got from the investigation of "Readiness and assessment of mucoadhesive microspheres of amoxicillin and rabeprazole for gastric ulcer" gives the accompanying end. By concentrating all the exploratory after effects of the readied microspheres it tends to be presumed

Table 6: Regression co-efficient (r2) values of different kinetic models and diffusion exponent (n) of Peppas model for Amoxicillin and Rabeprazole microspheres

Formulation	Zero order	First order	Higuchi Matrix	Peppas plot	
				r^2value	‗n'value
F1	0.976	0.905	0.934	0.986	0.426
F2	0.989	0.939	0.941	0.982	0.403
F3	0.990	0.941	0.980	0.985	0.421
F4	0.976	0.985	0.981	0.990	0.430
F5	0.966	0.938	0.961	0.991	0.397
F6	0.978	0.952	0.979	0.993	0.440
F7	0.989	0.979	0.981	0.991	0.408
F8	0.990	0.931	0.980	0.983	0.421

Table 7: Stability studies -% entrapment efficiency and *in vitro* release after 30 days storage

Formulation code	4 °C±1		25±2 °C and 60±5% RH		37±2 °C and 65±5% RH	
	% EE	**%CDR At 10h**	**% EE**	**% CDR at 10h**	**%EE**	**% CDR at10 h**
MF4	85.94	89.64	87.62	90.09	88.98	95.16

that Amoxicillin and Rabeprazole can be effectively defined by emulsification dissolvable vanishing strategy utilizing mucoadhesive polymers.

The IR range of unadulterated medication and medication polymer blend uncovered that there was no collaboration among polymer and medication. The readied microspheres were round with smooth surface and the yields of microspheres were exceptionally high. The ensnarement productivity and medication stacking were acceptable in all the cases; this recommends that enhanced boundaries were utilized in the technique for plan. *In vitro* mucoadhesion study exhibited that microspheres of MF4 detailing clung to the bodily fluid layer to a more prominent degree than different definitions.

In vitro drug arrival of microspheres displayed two sorts of delivery design for all microspheres with starting burst discharge impact, which might be credited to the medication stacked on to the outside of the particles. Generally speaking, the bend finding away into different numerical models were discovered to be inside indicated limits and the in vitro arrival of plan was best fitted to Zero-request energy.

Based on molecule size, drug content, Scanning Electron Microscopy, IR study, *in vitro* discharge studies and its active information, it was inferred that detailing MF1 was the upgraded definition.

The soundness investigations of plans MF4 demonstrated that 4°C is the appropriate temperature for capacity of mucoadhesive microspheres of Amoxicillin and Rabeprazole. Consequently, at last it was reasoned that the readied mucoadhesive microspheres of Amoxicillin and Rabeprazole can be considered as one of the promising plan strategy for gastro

retentive medication conveyance framework and subsequently can be successfully utilized in restorative administration of Gastric ulcer. Further detailed investigations are required to establish a large scale technique for industrial production.

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