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Research Article

DEVELOPMENT AND EVALUATION OF NOVEL COMPRESSION COATED TABLETS OF LEVOFLOXACIN AND RABEPRAZOLE USED IN THE TREATMENT OF PEPTIC ULCER DISEASE

Jagannath. M[1] , Mallikarjuna Gouda. M[*1], Somashekar Shyale[2], Shanta kumar S.M[1]
[1]V.L.College of pharmacy, Raichur, Karnataka – 584103
[2]H.S.B.P.V.T, Faculty of pharmacy, Kashti, Maharashtra, India
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Corresponding author's email: mkgouda0102@gmail.com

Abstract: Objective of present Study is to develop floating core in coat tablet in treating peptic ulcer disease. Rabeprazole and levefloxacin was used as model drug. The powder or granular bed is evaluated for pre compressional characteristics. The core tablet containing rabeprazole is prepared by direct compression and the coat granules containing leveofloxacin is prepared by wet granulation method, core tablet is compression coated with levofloxacin granules. The tablet is evaluated for compressional characteristics like thickness, diameter, hardness, buoyancy, floatation duration and studied *in vitro* dissolution in SGF and SIF in modified dissolution apparatus and studied the effect of different diluents like mannitol and MCC on release of rabeprazole in core tablet, HPMCK4M, Guar gum, Xanthan gum diluents on levofloxacin release in coat. The release of rabeprazole in Cr 2 is grater than Cr 1 because the mannitol is hydrophilic absorbs water and higher dissolution. The release of levofloxacin from coat containing HPMC K4M is higher by burst effect fallowed release in guar gum offering lesser resistance to molecular path than Xanthan gum. The above results indicate that floating core in coat tablet containing Guar gum and Xanthan gum as diluents are potential in the treatment of peptic ulcer disease.

Key words: Floating drug delivery system, Guar gum, Xanthan gum, Core tablet, Simulated intestinal fluid.

INTRODUCTION

Peptic ulcer is an erosion in the lining of the stomach or duodenum and peptic ulcer is located in the stomach it is called a gastric ulcer. Normally, the mucosal lining of stomach and small intestine protects against the irritating acids produced in stomach. For a variety of reasons (NSAIDS, Heredity) the protective mechanism becomes faulty, leading to a breakdown of the lining of mucosa causing gastritis or ulcer. The most common causes of such damage is infection of the stomach with a bacterium called *Helicobacter pylori*, [1] and other causes are alcohol, smoking etc. *Helicobacter pylor*i are gram negative, aerobic or microaerophilic, spiral shaped *bacilli*, found in the stomach which colonizes its host by living in the interface between the surface of gastric epithelial cells and the overlying mucus gel layer [2]. Rabeprazole and Levofloxacin are successfully used in the treatment of peptic ulcer. Rabeprazole is a proton pump inhibitor that suppresses gastric acid secretion through an interaction with H^+ / K^+ - ATPase in gastric parietal cells. Rabeprazole is effective in the treatment of various peptic diseases, including gastric and duodenal ulcer, gastro esophageal reflux disease and Zollinger – Ellison syndrome. The recommended adult dosage is 20 – 40 mg once daily [3, 4, 5] . Levofloxacin is a broad spectrum antibacterial agent with a recommended adult dosage of 500 mg once daily [6, 7, 8] . The current treatment for peptic ulcer is multiple drug regimen. Currently rabeprazole and levofloxacin are available as separate unit dosages. Patients need to be consume a unit at one time of administration.

Most of the proton pump inhibitors cannot sustain the lower acidic pH of stomach and antibiotics are relatively well absorbed from stomach. Compression coated tablets was recently renewed system to deliver a drug in a pulsatile way, at predetermined times following oral administration. Compression coated tablet prepared by placing granules half the weight of tablet in die, the core tablet placed at the center in die and remaining weight of the granules placed over the core and compressed with sufficient pressure in tablet punching machine [9, 10]. Therefore in this investigation, planned to formulate a compression coated tablet containing the rabeprazole an inner core and levofloxacin in outer coat unit. It was contemplated that by delivery both the drug from one unit help in maintaining the drug *in vivo* would be patient compliance.

MATERIAL AND METHODS

Material

Rabeprazole Sodium and Acryl EZE, Microcrystalline cellulose, Hydroxy propyl cellulose, Crass carmellose sodium, Aerosil, Xanthan gum were obtained as complimentary sample from Danmed pharmaceuticals Pvt Ltd, Hyderabad, Levofloxacin was received as a gift sample from alkem laboratories Ltd, Mumbai. Sodium starch glycolate, starch I.P, Citric acid, talc and magnesium sterate were purchased from S.d. Fine chemicals limited Mumbai. HPMC K4M was obtained from Himedia laboratories, Pvt Ltd, Mumbai. Guar gum was obtained from Aldrich, USA. Himedia laboratories, Pvt Ltd, Mumbai. Sodium carbonate was obtained from nice chemicals Pvt Ltd, Cohin.

Methods

Analytical method used for the estimation of rabeprazole and levefloxacin in bulk or in tablets.

Stock solution of rabeprazole (100 µg/ml) is prepared by dissolving exactly weighed 10mg of drug in 100ml distilled water. Aliquits of 2 – 10 ml of standard solutions were transferred into series of 10ml volumetric flask and volume in each flask adjusted with distilled water to get concentration range of 2 – 10 µg/ml. The resulting solutions absorbances were measured at λ_{max} of 277 nm against blank distilled water. The calibration curve was constructed by plotting absorbance versus concentration. Linearity of calilibration curve was studied in concentration range 2 - 10 µg/ ml. Similarly the levefloacin standard solution of 2, 4, 6, 8, 10 µg/ ml are prepared by diluting stock solution of (100 µg/ml) with distilled water. The solutions absorbances were measured at λ_{max} of 291.2 nm against blank of distilled water. Calibration curve was constructed by plotting absorbance versus concentration. Linearity of the calilibration curve was studied in concentration range 2 - 10 µg/ ml.

Method used for characterization of drug

The melting point of drug was determined in a digital point melting apparatus (n= 3). The solubility of both the drugs were studied in distilled water and in different pH buffers (2.5, 7.5, 8.0, and 9.0) according to method proposed by Diez et. al [11]. The filtrate solutions were suitably diluted with distilled water and absorbance was measured in a U.V. Spectrophotometer.

Method of preparation of core in coat tablet

The rabeprazole formulation constituting core of the tablets as shown in table 1 were prepared by direct compression technology. Ingredients were weighed accurately, milled and passed through sieve # 100 / 120 and then thoroughly blended and then compressed in a 10 station tablet punching machine using 6 mm flat punches at a pressure of 3 kg / cm ^{2}. The Core tablets were enteric coated in a kalweka HD coating pan so as to build 10% weight with Acryl Eze. The levofloxacin formulations were prepared by wet granulation technology as shown in table 2. Ingredients were weighed accurately, milled and passed through sieve # 100 / 120 and then thoroughly blended powder was granulated with water and starch paste (10% w/w) as binder to produce wet mass. The wet mass was passed through sieve 16, dried and again passed through mess # 20. Later talc and magnesium stearate as required were incorporated and blended. After adding the glidents and lubricants, half the weight of coat granules containing levofloxacin was placed in die cavity (13 mm) and then the core tablet of rabeprazole was placed into the same die cavity, the core tablet was manipulated and centered. The remaining half of the coat granules was placed over the core tablet so that the core is completely and uniformly surrounded by the coat granules and was then punched in a 10 station Rotary tablet press (PP1D, Chamunda India).

Evaluation of rheological properties of powder bed/granules

The powder beds of core and also coat powder were characterized for angle of repose, bulk density and compressibility index by using standard techniques. The experiment was repeated at least 3 times and average was computed.

Angle of repose was determined by measuring the height and radius of the heap of the powder / granule bed. A cut stem funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the plane. Powder / granule was placed in the funnel and allowed to freely. With the help of vernier calipers (Mitutoyo, Japan) the height and radius of the heap were measured and noted.

$$\tan \Ø = h/r$$

h = height of heap of powder/granule bed.

r = radius of heap of powder/granule bed.

Bulk density was determined (Konark instruments, India) by placing the powder/granules blend in a measuring cylinder and the total volume was noted. The weight of powder/granule bed was determined in a Dhona 200 D electronic balance. Bulk density was calculated by using the formula.

$$\text{Bulk density} = \frac{\text{Total weight of powder/granules}}{\text{Total volume of powder/granules.}}$$

Compressibility index was determined by placing the powder / granules in a measuring cylinder and the volume (V_o) was noted before

tapping. After 100 tapping again volume (V) was noticed. The compressibility index calculated according to the equation given below
Compressibility index = $(1-V/V_o)$ X 100

Evaluation of compressional characteristics of Core in coat tablets

Core in coat tablets were evaluated for Thickness, Diameter, Hardness (Pfizer hardness tester) Density of tablet, Disintegration time of tablet, *In vitro* buoyancy, *In vitro* dissolution studies.

The tablets were evaluated for their hardness using Pfizer hardness tester. Average of three reading were taken and tabulated (n = 3).

Disintegration time of tablet was determined by placing one tablet in each of the six tubes of the basket and operated the apparatus, using pH 9.0 buffers solution maintained at 37 $\pm$ 2^0 C. At the end basket was lifted from the fluid, and tablets were observed. All the tablets disintegrated completely[12] .

The *in vitro* buoyancy was determined by floating lag time, the buoyancy of tablets was studied at 37 ± 0.5 ^{0} C, in 100 ml of 0.1N HCL. A glass beaker containing 100 ml of 0.1 N Hcl was taken, in which a tablet was placed for observation. The duration of time taken for the tablet to float was determined as floating lag time. The total duration for which a tablet remains floating on the surface of fluid was recorded as duration of floatation. Average of three readings were taken (n=3) [13].

The drug content in each formulation of rabeprazole was determined by crushing the core tablet into powder in a mortar and powder equivalent to 100 mg of drug was taken in a volumetric flask containing pH 9.0 buffer and kept aside with constant shaking for 24 hours to extract the total drug present in the tablet. Then the absorbance of the solutions was measured against at λ_{max} of 277 nm against drug devoid pH 9.0 buffer as blank (n = 3).

The compressional coat of levofloxacin was carefully separated from core tablets and crushed into powder in a mortar and powder equivalent to 250 mg of drug was taken in a volumetric flask containing distilled water and kept aside with constant shaking for 24 hours to extract the total drug present in the tablet. Then the absorbance of the solutions was measured after suitable dilution at λ_{max} of 291.2 nm against blank of distilled water (n = 3).

The *in vitro* dissolution for core in coat tablet was studied in modified dissolution apparatus suggested by Mukesh C et al., [14] A modified dissolution apparatus was fabricated from a 100 ml glass beaker, by attaching an S-shaped side arm (glass tube) and capable of holding 70 ml of dissolution medium. The medium was stirred with magnetic stirrer at a speed of 50 rpm. The temperature of the medium was maintained at 37 $\pm$ 0.5 ^{0} C. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min. The tablet was placed into muslin sac and suspended in the dissolution media. From the burette, simulated gastric fluid was added at a rate of 2 ml/min. Samples of 1 mL were collected at predetermined time intervals for 2 h, the dissolution was further carried out with the same tablet by replacing the dissolution media with buffer pH 9.0 for 6 h and samples of 1 ml were withdrawn periodically and analyzed spectrophtometrically. All the studies were carried out in triplicate, (n=3).

RESULTS AND DISCUSSIONS

The absorbance maxima of rabeprazole 272.2 nm and levofloxacin 291.2 nm obtained during this study corroborates with the literature value [15, 16]. The analytical method developed was validated for linearity, accuracy and precision. The developed method was found to be robust, simple, linear, accurate and precise. Melting points of rabeprazole and levofloxacin were found to be 137 ^{0} C and 222 ^{0} C respectively nearer to literature value [17, 18]. The solubility of rabeprazole was found to be 0.085 mg/ml in pH 2.5, 100.4 mg/ml in distilled water, 0.395 mg/ml in pH 7.5 and 0.567 mg/ml in pH 9.0 at 20˚ C. It was observed that, rabeprazole in the lower pH media (below pH 9) turns dark and degree of darkness is more in lower pH than in higher pH. It was also observed from the results that, the solubility of rabeprazole increase with increase in alkaline pH. Hence buffer of pH 9.0 was used as SIF for *in vitro* dissolution studies. The solubility of levofloxacin in distilled was found to be 51mg/ml and 2.10 mg/ml in pH 2.5, 44.18 mg/ml in pH 7.5 and 53.72 mg/ml in pH 8.0 at 20 ^{0}C . The solubility was found to increase with increase in pH. Albeit the solubility of levofloxacin is high in distilled water (pH 7.0), water alone cannot simulate the gastric fluids, hence buffer of pH 1.2 was used as SGF during *in vitro* dissolution studies.

Table 1: Formulae of Core tablets of Rabeprazole

Ingredients	Formulation (mg)	
	Cr 1	Cr 2
Rabeprazole Sodium	21.00	21.00
Sodium Starch glycolate	03.00	-
Microcrystalline cellulose	76.00	-
HPC – LH 11	-	16.00
Cross carmellose sodium	-	03.00
Aerosil	-	1.00
Mannitol	-	55.00
Talc	-	2.00
Magnesium stearate	-	2.00
Total tablet Weight (mg)	100 mg	100 mg

Table 2: Formulae of Coat tablets of Levofloxacin

Ingredients	Formulation (mg)					
	Ct 1	Ct 2	Ct 3	Ct 4	Ct 5	Ct 6
Levofloxacin	250	250	250	250	250	250
Starch paste 10%	50	50	50	50	50	50
HPMC K4M	80	-	-	62.5	-	-
Guar gum	-	80	-	-	62.5	-
Xanthan gum	-	-	80	-	-	62.5
$NaHCO_3$	60	60	60	70	70	70
Citric acid	45	45	45	52.5	52.5	52.5
Talc % w/w	10	10	10	10	10	10
Magnesium stearate % w/w	5	5	5	5	5	5
Total weight Tablet (mg)	500	500	500	500	500	500

MCC is hydrophobic in nature and mannitol is hydrophilic, hence to study the influence of these two polymers on rabeprazole release, rabeprazole tablets (100 mg) were dispensed with two different diluents, MCC (Cr 1) and Mannitol (Cr 2). To protect rabeprazole from gastric contents the core tablets were coated with Acryl EZE. The powder beds prepared for direct compression of rabeprazole core tablets were evaluated for flow properties. The angle of repose (θ^0) was found to be 32.06 ^{0} and 27.31^0 respectively. Bulk density was found to be 0.319 gm/cc and 0.416 gm/cc respectively for Cr 1 and Cr 2. Compressibility index of directly compressible powder bed of rabeprazole were found to be less than 15 % for both Cr1 and Cr 2 powder bed. The index was observed to be 12.85 % and 11.65 % respectively. These values indicate that the prepared powder bed exhibits good flow properties. The thicknesses of the compressed core tablet were found to be 2.81 mm to 2.74 mm. The diameter was also found be 7.4 mm. The hardness of tablet compacts Cr 1 and Cr 2 were found to be between 3.3 $\pm$ 0.08 Kg/cm^2 and 3.0 0.33 Kg/cm respectively, indicating that various batches of rabeprazole core tablets were uniform, consistent and reproducible. Drug content of both formulations was found to be 96.14% and 97.09% indicating content uniformity.

Table 3. Characterization of drug

	Melting point	Solubility (mg/ml)				
Rabeprazole	137 ^{0} C	pH 2.5 0.085	Distilled water 100.4	pH 7.5 0.395	pH 8.0 -	pH 9.0 0.567
levofloxacin	222 ^{0} C	2.10	51	44.18	53.72	-

Table 4. Accuracy and Precision studies of Rabeprazole

Drug	Formulation	Amount of Drug added (mg/ml)	Amount recovered (mg/ml)	Accuracy	Precision
Rabeprazole Sodium	Cr -1	21. 0	20.19	96. 14%	0.11
	Cr -2	21. 0	20. 39	97.09%	0.26

Table 5. Accuracy and Precision studies of Levofloxacin

Drug	Formulation	Amount drug added (mg/ml)	Amount Drug recovered (mg/ml)	Accuracy	Precision
levofloxacin	Ct-1	250.0	248.6	99.44%	0.163
	Ct-2	250.0	249.0	99.6%	0.245
	Ct-3	250.0	245.94	98.6%	0.18
	Ct-4	250.0	243.69	97.35	0.172
	Ct-5	250.0	245.49	98.19	0.163
	Ct-6	250.0	244.57	97.82	0. 269

The granules prepared for compression of coat are evaluated for flow property. The angle of repose (ɵ ^{0}) was found to be between 29.6 ^{0} to 33.17 ^{0} before incorporating glidants. Similar after addition of glidants, talc and magnesium stearate (2:1) showed reduced angle of repose varying between 28.22 ^{0} and 30.38 ^{0}. Bulk density was found to be around 0.5 gm/cc respectively for all coat granules. Carr's Compressibility index of coat granules containing levofloxacin was observed to be between 5.4% and 8.3% for Ct 1 through Ct 6 respectively. The above results indicate that granules are easily compressible and the bed flows unhindered. The thickness of the compressed final core in coat tablets were found to be between 5.20 to 5.46 mm .The diameter was found to be 13.27 to 13.48 mm.The hardness of tablets Ct 1 through Ct 12 was found to be varying between 5.0 $\pm$ 0.43 Kg/cm^2 and 7.6 $\pm$ 0.163 Kg/cm^2. The above results indicate that, various batches of levofloxacin coat tablets were uniform, consistent and reproducible. The calculated densities were found to be between 0.722 $\pm$ 0.05 and 0.781 $\pm$ 0.015 respectively for Ct 1 through Ct 6. The densities of the tablets are less than 1 therefore it was understood that all the coated tablets would remain buoyant over the surface of the GI fluids. Studies were carried to study the amount of sodium bicarbonate: citric acid, but keeping the ratio constant as optimized in a previous study in our lab, at 1: 0.75. It was found that, an amount of 70 mg of sodium bicarbonate and 52.5 mg of citric acid (1: 0.75) would be sufficient to make the 600 mg tablet and to remain buoyant on the surface for a long period (>4 h).

Table 6. Evaluation of rheological and compressional characteristics of Core tablets of rabeprazole (n=3).

Formu lation	Compres si bility index	Bulk density g/cc	Angle of repose ($^o\theta$)		Hardness Kg/cm^2	Density g/cc	Floatatio n lag time (mn)	Flotatio n time (h)	Drug content (mg)
			Before adding glidents	After adding glidents					
Ct 1	7. 86%	0. 56	30.92	28. 56	6. 70	0.722	11. 1	-	248. 0
Ct 2	8. 3%	0. 55	33.17	30. 38	5. 73	0. 81	26. 55	6	249. 0
Ct 3	5. 55%	0. 50	29.60	28. 77	5. 73	0.771	31. 2	4. 31	245. 94
Ct 4	2. 73%	0. 50	30.1	28. 22	6. 60	0.726	10. 22	-	243. 69
Ct 5	7. 7%	0. 63	31.8	27. 4	7. 30	0.736	21. 39	5. 48	245. 49
Ct 6	5. 4%	0. 52	31.75	28. 4	5. 80	0.736	35. 42	4. 1	244. 57

Table 7. Evaluation of rheological and compressional characteristics of Coat tablets of levofloxacin (n=3).

Formu lation	Compressi bility index	Bulk density g/cc	Angle of repose ($^o\theta$)	Hardness Kg/cm^2	Density g/cc	Disinti gration Time (mn)	Drug content (mg)
Cr 1	12. 85 %	0. 319	$32 .06^0$	3. 3	0. 813	8	20. 19
Cr 2	11. 65 %	0. 416	$27. 31^0$	3. 0	0. 86	8	20. 39

The floatation study of coat reveals that, The Coat containing HPMC K4M as diluent disintegrated within 12 min of floatation studies. The coat containing Xanthan gum as diluent shown highest lag time of nearly 30 to 35 min since the density of xanthan gum is higher and the guar gum as diluent shown lag time of 20 to 27 min is lesser than the xanthan gum coat. The duration of floating were shown highest in coat containing guar gum is 5 ½ h to 6 ½ h and the coat containing Xanthan gum as diluent showed floating duration of 4 h to 4 ½ h. It is assertive therefore both guar gum and Xanthan gum polymers are potential excipients for the FDDS. Drug content of all formulations containing HPMC K4M, Guar gum, Xanthan gum as diluent were in the range of 99.77% - 97.57% indicating content uniformity. The *in vitro* dissolution study was conducted in a modified dissolution apparatus. Initial dissolution studies were carried out in dissolution medium of SGF for 2 h, during which the levofloxacin present in the coat was released.

The coat formulation containing gas generating agent in the ratio of 60: 45 mg is sufficient for 600 mg tablet to float on the surface of gastric fluid. The amount of levofloxacin released from coat formulation containg HPMC K4M (16%) as diluent is 91.6 % which is significantly higher as drug release is by burst effect. The levofloxacin released from coat with guar gum (16%) as diluent is 90% which is lesser than HPMC K4M, as it absorbs water start swelling, viscosity of the gel increases which offers resistance to the molecular path, hence lesser slope but the linearity of the curve shows zero order release rate. Similarly the levofloxacin release from coat of Xanthan gum (16%) as diluent is 81.2 %, which is far lesser than HPMC K4M and guar gum. As Xanthan gum absorbs water the viscosity of the gel becomes higher and tougher. Hence offer higher resistance to molecular path than the previous gums, hence slope is lesser of three gums but the linearity of the curve shows zero order release.

Further increased the amount of gas generating agent in coat formulation in ratio of 70: 52.5 mg and studied the levofloxacin release from coat. The amount of levofloxacin released from coat formulation containg HPMC K4M (13 %) as diluent is 93.04 % which is significantly higher as drug release is by burst effect, release owing to probably diffusion and erosion. Levofloxacin release from coat with guar gum (13 %) as diluent is 89.36 % which is lesser than HPMC K4M, absorbs water start swelling, viscosity of the gel increases, offering resistance to the molecular path, hence lesser slope. Similarly the levofloxacin release from coat of xanthan gum (13 %) as diluent is 81.6 %, which is far lesser than HPMC K4M and Xanthan gum. As the amount of gas generating increased the release rate is higher, as there is less resitance to molecular path and drug released by diffusion and erosion.

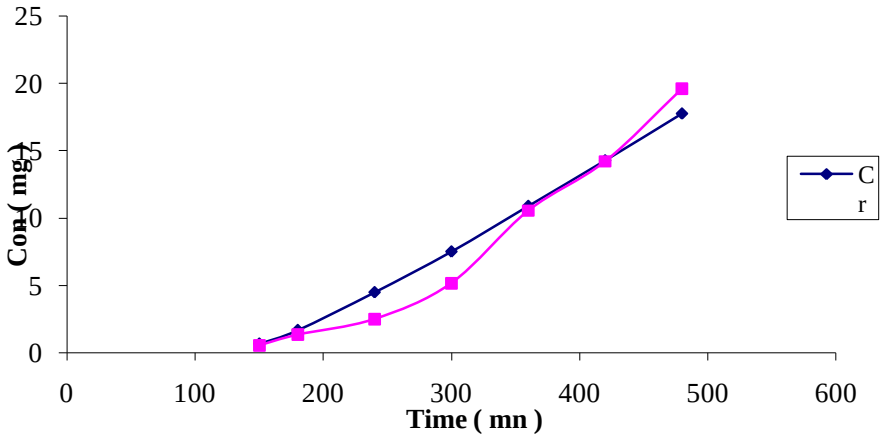

Fig 1. *In vitro* release of rabeprazole in SGF from respective formulation Cr 1, Cr 2.

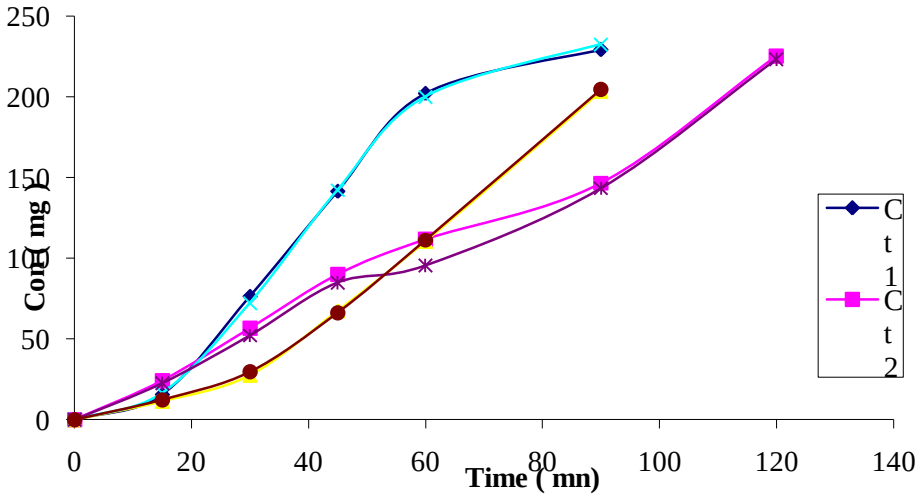

Fig 2. *In vitro* release of levofloxacin in SIF from respectively formulation of Ct 1, Ct 2, Ct 3, Ct 4, Ct 5, Ct 6.

After 2 hour the core in coat tablet peeled off coat and released core tablet. Later *in vitro* dissolution of core formulations were carried out with the same intact tablet in buffer pH 9.0 to study the release of rabeprazole from core formulation. The release of rabeprazole from Cr1 containing microcrystalline cellulose as diulent is 88.01 %. The release of rabeprazole from Cr 2 containing mannitol as diluent is 96.12 % into dissolution media. The *in vitro* results shows that, the release rate of rabeprazole from Cr 2 is better than Cr1 as mannitol is hydrophilic in nature helps in improving the dissolution of drug. The data obtained were subjected to regression analysis (r) by least squares method, and statistically ANOVA was preformed on *in vitro* data. A value of $p < 0.05$ was considered statistically significant. The zero order plot curve of all formulation is fairly linear, as indicated by high regression coefficient (r) 0.956 - 0.998. Stability study conducted according to ICH guidelines at 40 ^{0} C / 75% RH indicates that rabeprazole concentration declines rapidly, the excipient microcrystalline, mannitol present in core do not help in protecting the drug from deterioration. The amount of levofloxacin decreased does not exceed 10 % of the initial drug content. It was hence ascertained that, by adding overages, can retain the labeled amount of drug.

CONCLUSIONS

The effervescent based floating drug delivery system is a promising approach to achieve

buoyancy of core in coat tablet. Analytical method developed for the quantization of both drug rabeprazole and levofloxacin was found to be accurate, precise and linear. Density of the tablets was less than 1, thereby assisting in floating of the dosage form on the surface of the dissolution medium. The rabeprazole core tablet coating with Acryl EZE was found to protect from acidic environment and drug release is higher in core 2 as the diluent is hydrophilic in nature. Release of levofloxacin from coat formulations containing HPMC K4 M as diluent is by burst effect as compared to other diluents guar gum and xanthan gum. The above studies indicated that, gastro retentive floating core in coat tablets of xanthan gum and guar gum are potential oral dosages. Such a dosage form would be effective in the treatment of peptic ulcer disease since it overrides the multi drug therapy.

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