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Formulation and evaluation of caplet containing sustained release aceclofenac and rabeprazole tablets

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ABSTRACT

Caplet containing Aceclofenac- sustained release (SR) and Rabeprazole sodium – enteric coated (EC) tablets was developed. Aceclofenac is a non steroidal anti inflammatory drug (NSAIDS) having poor water solubility and short t1/2 of 4 hours hence formation of its solid dispersion further sustaining its release to give good dissolution after release for a specific period of time. Rabeprazole is an acid- labile, proton pump inhibitor thus enteric coated by using CAP to prevent its degradation in acidic environment and HPMC to sustain its release too.

Key words: sustained release tablets, delayed release tablet, solid dispersion, enteric coating tablet, Aceclofenac, Rabeprazole sodium.

INTRODUCTION

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) modified analog of Diclofenac. It is used for the relief of various types of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. This drug works by blocking the action of a substance in the body called cyclo- oxynase (COX).

Aceclofenac dose is 100 mg twice daily. It should not be given to people with porphyria or breast-feeding mothers, and is also not recommended for children. It is a cytokine inhibitor. COX is involved in the production of prostaglandins (chemicals in the body) which cause pain, swelling and inflammation in the body. Aceclofenac is thglycolic acid ester of diclofenac. The incidence of gastric ulcer of aceclofenac has been reported to be significantly lower than that of the other frequently prescribed NSAIDs, in adverse effect it is 2-folds lesser than naproxen, 4-folds lesser than diclofenac, and 7-folds lesser than indomethacin[1]. Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anti-cholinergic or histamine H2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H^+/K^+ATPase (hydrogen-potassium adenosine triphosphatase) at the secretory surface of the gastric parietal cell.

MATERIALS AND METHODS

Aceclofenac and rabeprazole and all other excipients and chemicals were a gift sample from Akums drug and pharmaceutical Pvt. Ltd., Haridwar, U.K, India.

Formulation of Aceclofenac solid dispersion:

Experimental design [2]
The formulation was formed using factorial design of two variable i.e mannitol and lactose: corn starch with Aceclofenac.

Table1. Formula for solid dispersion of Aceclofenac

S.No.	Formula	Drug: polymer ratio	Drug (mg)	Mannitol (mg)	Lactose:corn starch (1:0.5)
1.	**F1**	1:0.25	200	50	-
2.	**F2**	1:0.33	200	66.66	-
3.	**F3**	1:0.5	200	100	-
4.	**F4**	1:0.25	200		50
5.	**F5**	1:0.33	200		66.66
6.	**F6**	1:0.5	200		100

Preparation of solid dispersion of Aceclofenac[3, 4, 5, 6]
Carrier (Mannitol, Lactose and maize starch premix) were passed through sieve no 60. Aceclofenac and carrier each formulation, was mixed in polybag for 10 minute and kneaded thoroughly for 25-30 minute in a pestle and mortar by the use of ethanol and water in (1:1) ratio as solvent. The paste so formed was dried at 45 °C in hot air oven. Dried granules were pulverized through 14 mm mesh.

Formulation of sustained release Aceclofenac Tablet by using solid dispersion [7-10]
Preparation of core tablets
Granules were prepared using wet granulation method. Drug and other excipients were passed through # 80 and add sufficient quantity of binding agent slowly to get dough like mass. The mass was sieved through # 80 and dried at 45ºC for about 1 hrs. And then these granules were passed through # 20 and lubricated with magnesium stearate. Mixed blend was compressed into tablets on single punch tablet compression machine to a weight of 400 mg each with thickness of 4.46 ± 0.21 mm and diameter of 7.9 mm using shallow concave punch.

Table2. Formula for compressed Aceclofenac tablet

Ingredients	F1	F2	F3
Solid dispersion	300	300	300
MCC	40	45	50
Dicalcium phosphate	35	35	35
PVP k30	15	15	15
Purified water	q.s	q.s	q.s

Preparation of Coating solution:
Hydroxy Propyl Methyl Cellulose (E5 LV) was Dispersed in Isopropyl Alcohol and Stirred for 15 – 20 minutes until uniform dispersion was formed. Then slowly add Diethyl phthalate to the above solution under a constant stirring. In small quantity of methylene chloride, polyethylene glycol 4000 (Macrogol 4000) was then dissolved and added in above solution. Titanium Dioxide and Talc were also added to the above solution.

Then Methylene Chloride added with continuous stirring for 15-20 minutes. This solution was milled through colloid mill and rinsed the colloid mill with remaining Isopropyl Alcohol and Methylene chloride. And finally this solution was filtered through 100 mesh nylon cloth.

Table3. Formula for coating solution

Ingredient	F1	F2	F3
HPMC (E5 LV)	55	50	45
Diethyl pthalate	2	2	2
Propylene glycol- 4000	2	2	2
Talc	4	4	4
Titanium dioxide	5	5	5
Isopropyl dioxide	q.s	q.s	q.s
Methylene chloride	q.s	q.s	q.s

Preparation of enteric coated Rabeprazole tablets:

Preparation of Rabeprazole Sodium Tablet [11]

Rabeprazole sodium granules for tablet making were prepared by wet granulation method. Specified quantity of Rabeprazole, Polymers (Hydroxypropyl methylcellulose (HPMC) or Carbapol) and Avicel pH 102 were weighed according to the formula (Table 1) and transferred in a mortar and pestle and mixed thoroughly. The powder mass was mixed with 5% starch paste to obtain a sluggy mass and this was passed through sieve no. 12 to obtain granules. The granules prepared were dried at 45^0C for 4 h. The dried granules were screened through sieve no. 22 and stored for further studies. The specified quantity of magnesium stearate and talc were finally added and mixed just before compression of tablets. Ideal mixtures of granules were directly punched into tablets weighing about 200 mg containing 20 mg of Rabeprazole sodium, using rotary tablet compression machine. The different batches of Rabeprazole tablets were collected and stored in air tight containers.

Table4. Formula chart for rabeprazole SR tablets

Ingredients	F1	F2	F3	F4	F5	F6
Rabeprazole	20	20	20	20	20	20
HPMC	20	40	60	-	-	-
Carbopol				20	40	60
Avicil- 102	66	66	66	66	66	66
Starch paste 5%	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Talc	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4

Enteric coating of rabeprazole sodium compressed tablets by spray dried method:

For the coat, the tablets were coated by using Pan coating apparatus, and different in-process samples were taken to check if the target polymer weight gain was achieved. Coating was continued until complete polymer weight gain was achieved.

After the coating, the tablets kept a side for 10 min after which they were cured at 40 ◦C for 24h.

Table5. Composition of coating solution

Ingredient	Quantity (%w/w)
Cellulose acetate phthalate	6.0
Titanium dioxide	2.6
Diethyl phthalate	2.0
Acetone	59.4
Isopropyl alcohol	30.0

Evaluation of SR Aceclofenac tablets:[12-14]

Content uniformity

Ten tablets of each type of formulation were weighed and crushed in mortar and was dissolved in 100 ml of water. This was the stock solution from which l ml sample was withdrawn and diluted to 100 ml with 0.1N HCl. The absorbance was measured at wavelength 280 nm using double beam UV-Visible spectrophotometer.

Weight variation

Twenty tablets were selected randomly and weighed. Average weight of the tablet was determined. These tablets were weighed individually and the weight variation was determined.

Tablet hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usages are depends on its hardness. The hardness of tablet of each formulation was checked by using hardness tester. The hardness was measured in terms Newton.

Thickness

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier caliper. It was determined by checking ten tablets from each formulation.

Dissolution studies

Tablets of each formulation were subjected to dissolution rate studies. In-vitro dissolution studies were carried out to determine the drug release from various formulations. The release characteristic studies included the amount of drug released per hour up to 12 hours. Firstly check into acidic pH 1.2 and then in phosphate buffer.

Evaluation of EC Rabeprazole tablets [15-21]

Weight Variation

Twenty tablets were selected randomly and weighed. Average weight of the tablet was determined. These tablets were weighed individually and the weight variation was determined.

Tablet Hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usages are depends on its hardness. The hardness of tablet of each formulation was checked by using hardness tester. The hardness was measured in terms Newton.

Thickness

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier Caliper. It was determined by checking ten tablets from each formulation.

Drug Content

Five tablets were powdered in a mortar. Weighed accurately the quantity equivalent to 10 mg of Rabeprazole sodium and transferred to a 100ml volumetric flask containing few ml of phosphate buffer and mixed well, made up the volume up to 100ml with phosphate buffer. Pipette out 10 ml from this solution into another 100 ml volumetric flask and made up the volume with phosphate buffer 7.2 to produce stock solution of concentration 100 mcg/ml.

The above stock solution of drug was subsequently diluted with phosphate buffer 7.2 to get 2 mcg, 4 mcg, 6 mcg, 8 mcg and 10 mcg, of drug per ml. Then the absorbance of these dilute solutions was measured at a λ max of 287 nm by using double beam U.V. spectrophotometer against a blank of phosphate buffer 7.2

***In-vitro* Release Studies [22, 23]**

The *in-vitro* dissolution profile of the designed formulations was carried out using USP type I apparatus under conditions specified (Temp 37±0.5oC, at 100 rpm).As artificial gastric fluid, 0.1N HCl (pH 1.2) was used. The artificial intestinal fluid was prepared phosphate buffer (pH 7.2).

In Capsulation of Aceclofenac & Rabeprazole

Both formed tablet of rabeprazole and aceclofenac fill in capsule no 0 as both having light density as per specifications.

In Vitro Release of Combined Dosage Form: [24]

Finally caplet containing aceclofenac and rabeprazole tablet subjected for dissolution, designed formulations was carried out using USP type I apparatus under conditions specified (Temp 37±0.5^{0}C, at 50 rpm). The artificial intestinal fluid was prepared in borate buffer (pH 8).

The optimum batches were selected from developed formulation of Aceclofenac [SR] and Rabeprazole [EC]. The one mini- tablets from batch F3 of Aceclofenac [SR] and F2 one mini-tablet of Rabeprazole [EC] were filled in a capsule shell [Size 0] to form caplet. The drug release of Aceclofenac and Rabeprazole was performed in alkaline borate buffer [pH 8]. The bowels of dissolution apparatus were wrapped with aluminum foil to protect the drug released in media from light. 5 ml of aliquots of drug samples were removed at intervals of 1 hr, 2hrs, 3hrs, 4hrs, 6 hrs, 8 hrs, 10 hrs and 12 hrs. The samples were filtered through Whattman filter paper no.42 in amber colored vials. The aliquot samples were analyzed by RP-HPLC. Another set of caplet was subjected drug release in 0.1 N HCl to confirm there is no release or negligible release of Rabeprazole in acid stage for two hours.

The drug release of caplets was also studied separately in 0.1 N HCl for 2 hrs to confirm no or acceptable drug release in acid stage. The tablets from the acid medium were removed at the end of 2 hrs and the drug content of tablets was determined to confirm no or acceptable level [10%] of drug release in 0.1 N HCl.

RESULTS AND DISCUSSION

F6(drug+ lactose:corn starch ratio 2:1) show good dissolution release profile as compare to others formulation as well as from pure drug. We continued our work with formulation F6 for making sustained release tablet. F6 is selected for further film coating.

Table6. Tablet properties of core tablet of aceclofenac sustained release formulation

Formulation	Average weight (mg)	Diameter	Thickness (mm)	Hardness (Kg/cm^2)	% Friability
F1	400	10.10	4.4	9.25	0.0052
F2	396	10.24	4.5	9.34	0.0046
F3	397	10.25	4.6	9.85	0.0043

Table7. Comparisons of dissolution profile of different Aceclofenac tablet formulations

Time	F1 % release	F2 % release	F3 % release
1	15.72	15.72	28.018
2	26.32	29.29	32.68
3	37.14	40.75	46.91
4	52.03	56.03	59.43
6	56.25	59.43	61.76
8	60.28	64.31	69.62
10	64.52	68.77	87.87
12	79.38	81.50	99.12

Formulation F3 shows better release of 99.12 % till 12 hours in comparisons to other formulation

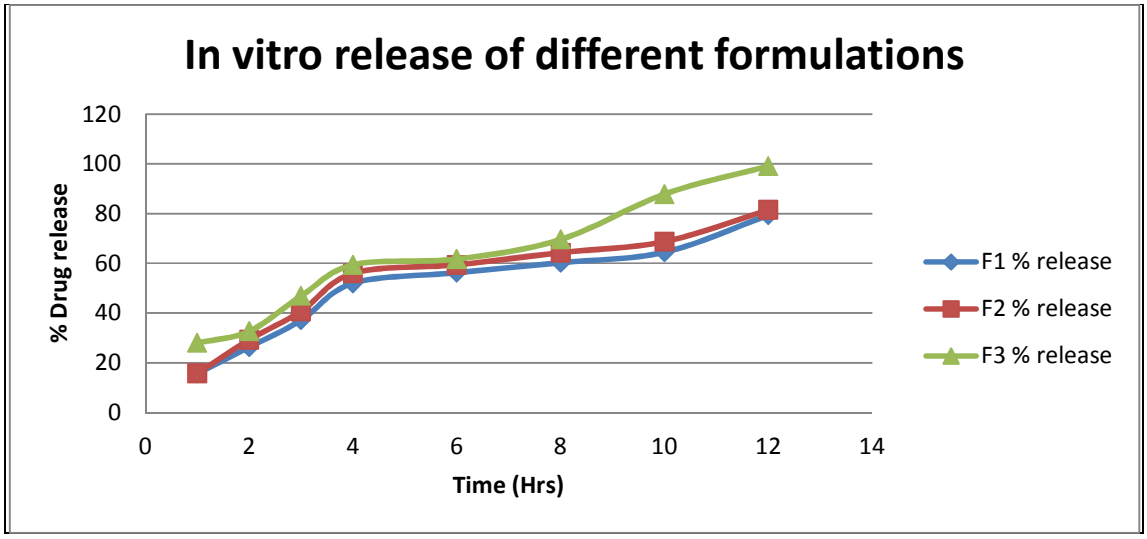

Fig1. Drug release profile of different formulations of aceclofenac in phosphate buffer

Table8. Comparisons of dissolution profile of different formulations of rabeprazole sodium tablet

Time	F1 % release	F2 % release	F3 % release	F4 % release	F5 % release	F6 % release
0.5	11.04	16.31	9.95	10.16	10.05	9.95
1	19.48	15.03	13.34	13.87	13.23	12.17
2	31.65	33.14	31.23	30	29.54	27.84
3	48.6	48.6	45.84	46.05	37.16	34.30
4	56.85	58.76	56.01	57	41.18	40.12
6	66.38	66.38	63.95	64.37	52.41	49.23
8	75.91	75.91	72.42	73.8	61.51	57.07
10	83.01	84.6	81.74	79.41	69.35	62.89
12	90.31	91.2	84.38	85.02	78.77	73.16

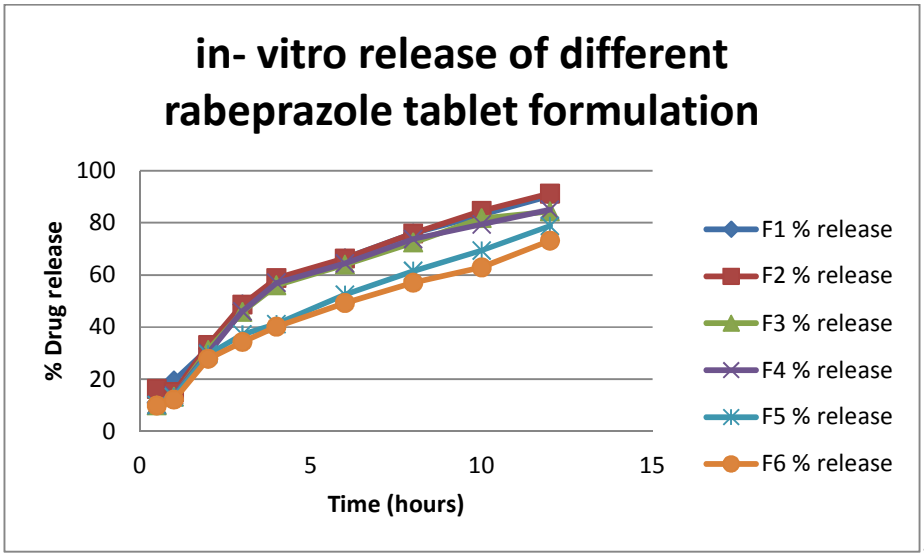

Fig2. Drug release profile of different formulations of rabeprazole

Table9. In vitro dissolution study of caplet

Time	Aceclofenac release %	Rabeprazole release %
1	28.018 ± 3.43	15.03± 3.65
2	32.68 ± 4.43	33.14± 5.34
3	46.91 ± 7.04	48.6± 7.73
4	59.43 ± 6.34	58.76± 6.43
6	61.76 ± 6.08	66.38± 6.21
8	69.62 ± 8.15	75.91± 7.34
10	87.87 ± 5.61	84.6 ± 6.51
12	99.12 ± 4.31	91.2 ± 4.12

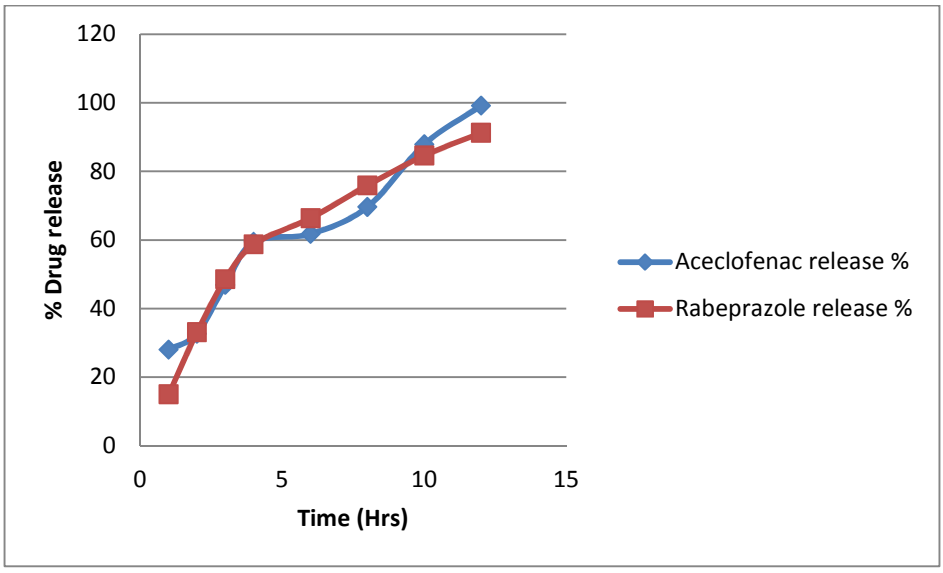

Fig 3: % release of both Aceclofenac and Rabeprazole in phosphate buffer

Both aceclofenac and rabeprazole showed 12 hour release with 99.12 and 91.2% respectively.

Drug release study

Table10. Drug release kinetics of an optimised formulation of Aceclofenac

Time	CDR%	Log CDR%	% drug remaining	Log of % drug remaining	Log T	$\sqrt{T}$
1	28.018	1.4437	71.95	1.8572	0.0000	1.0000
2	32.68	1.5142	67.32	1.8281	0.3010	1.4142
3	46.91	1.6712	53.09	1.72509	0.4771	1.7321
4	59.43	1.7740	40.57	1.6082	0.6021	2.0000
6	61.76	1.7907	38.24	1.5825	0.7782	2.4495
8	69.62	1.8427	30.38	1.4825	0.9031	2.8284
10	87.87	1.89438	12.13	1.0838	1.000	3.1623
12	99.12	1.9961	0.88	-0.0555	1.0792	3.4641

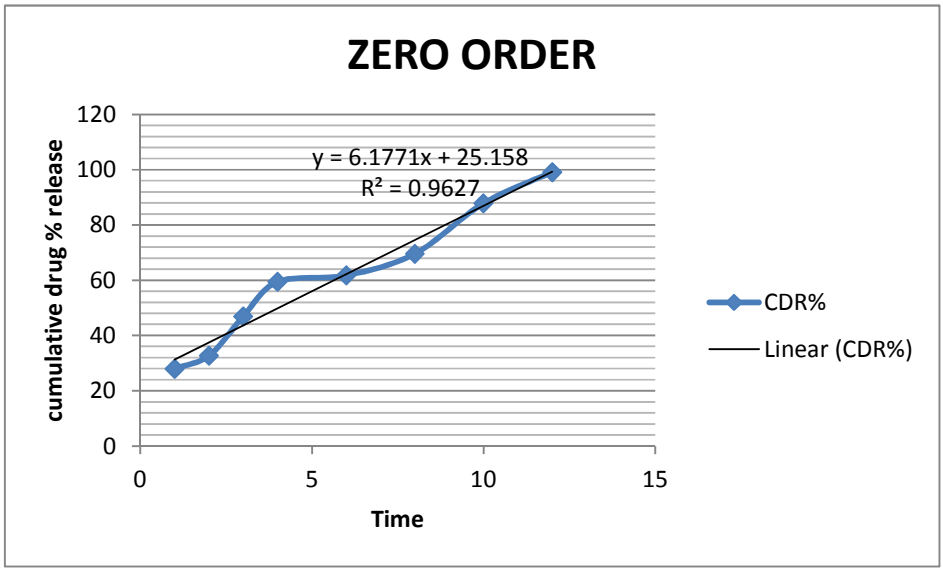

Fig4. Zero Order Release of Aceclofenac

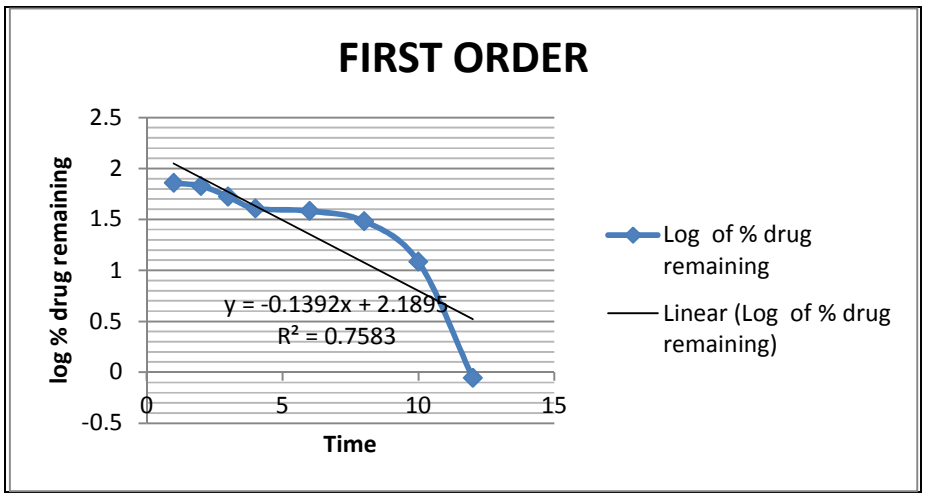

Fig5. First order release of aceclofenac

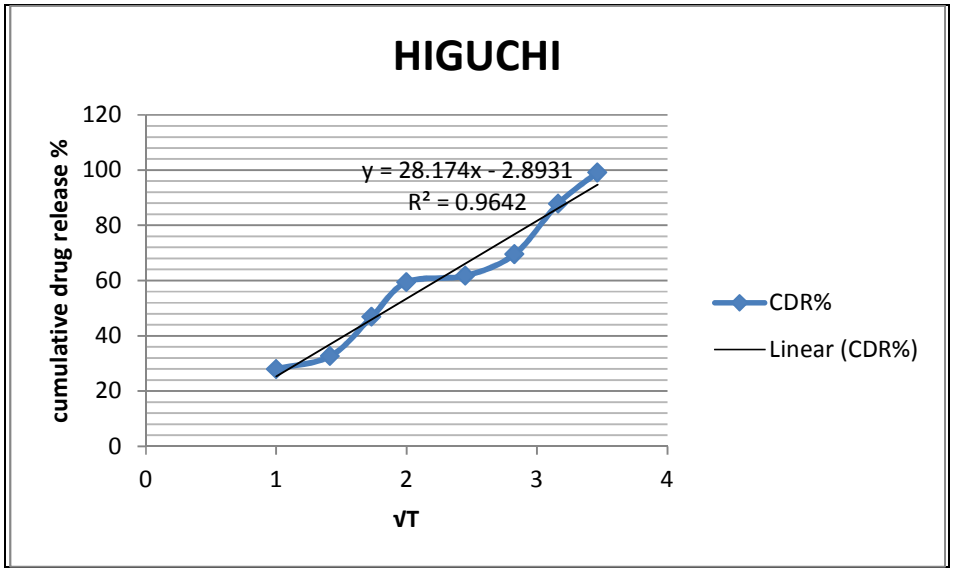

Fig6. Time1/2 Vs cumulative drug release Higuchi plot for F1

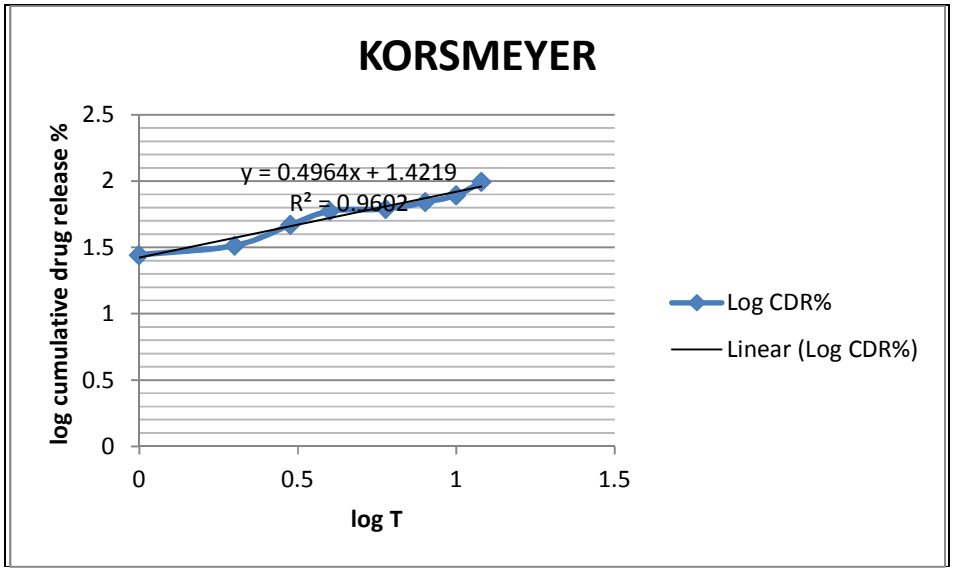

Fig7. Log t Vs log cumulative drug release Korse Meyer plot for F1

Table11. Drug release kinetics of an optimised formulation of Rabeprazole

Time	CDR%	Log CDR%	% drug remaining	Log of % drug remaining	Log T	$\sqrt{T}$
1	15.03	1.1176	84.97	1.9292	0.0000	1.0000
2	33.14	1.5203	66.86	1.8251	0.3010	1.4142
3	48.6	1.6866	51.4	1.7109	0.4771	1.7321
4	58.76	1.7690	41.24	1.6153	0.6021	2.0000
6	66.38	1.8220	33.62	1.5265	0.7782	2.4495
8	75.91	1.8802	24.09	1.3818	0.9031	2.8284
10	84.6	1.9273	15.4	1.1875	1.000	3.1623
12	91.2	1.9599	8.8	0.944	1.0792	3.4641

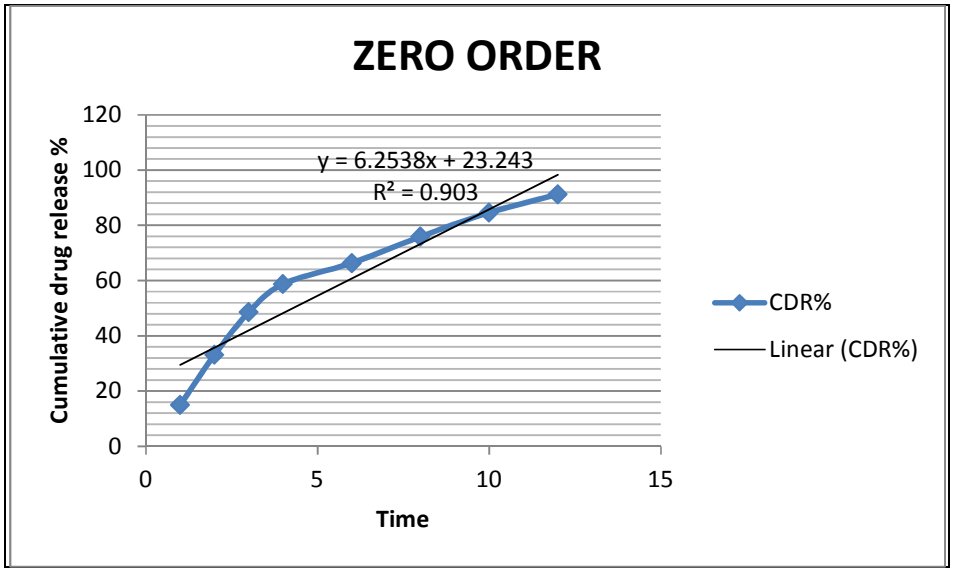

Fig 8. Zero order release of delayed release Rabeprazole

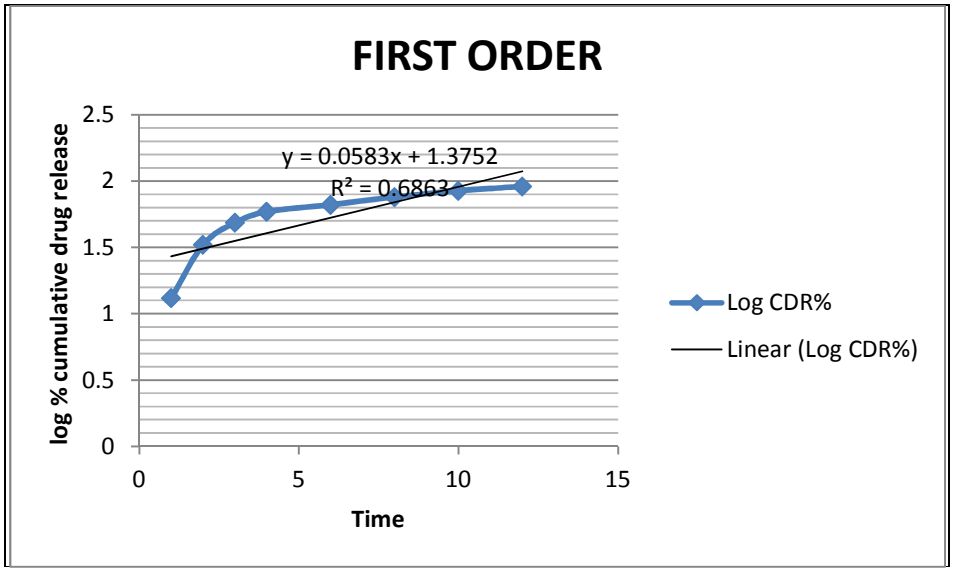

Fig9. First order release of delayed release rabeprazole

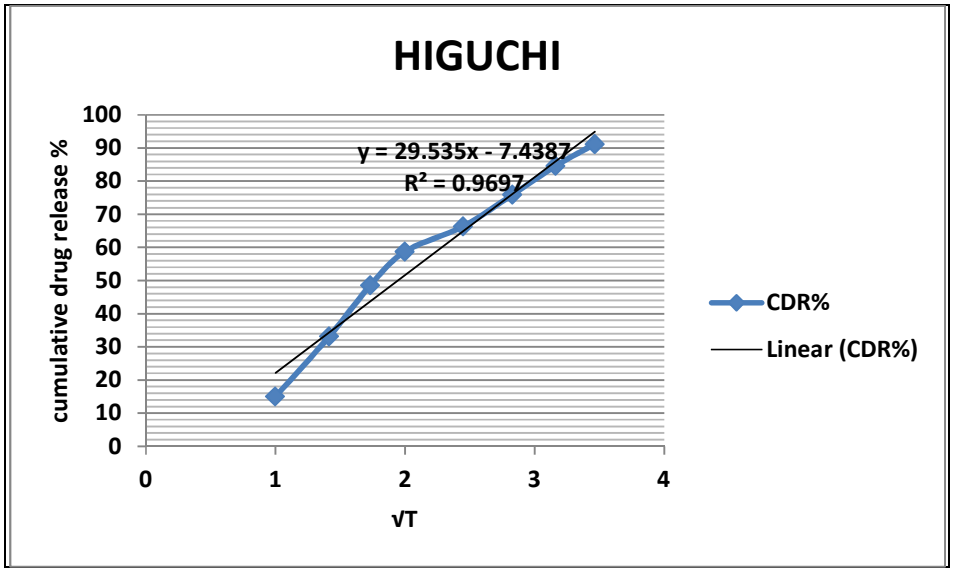

Fig10. Time 1/2 Vs cumulative drug release Higuchi plot for Rabeprazole

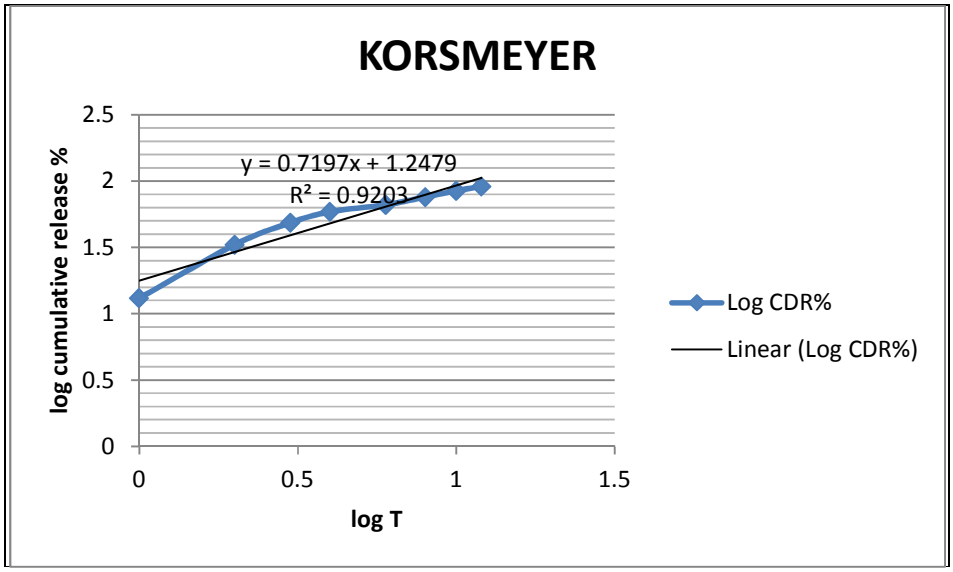

Fig11. Log t Vs log cumulative drug release Korse Meyer plot for Rabeprazole

CONCLUSION

In this study I present a novel dosage form of sustained release. These caplets were prepared by combining Aceclofenac tablet together with rabeprazole in capsule. A drug with a low solubility as well as short t1/2 of Aceclofenac is maintained by making solid dispersion of Aceclofenac before sustaining it. It will give a long 12 hour release in alkaline pH with increased dissolution rate. Rabeprazole in enteric coated formulation prevent it from acidic environment together with sustained release of 12 hour in alkaline pH.

The dissolution of Aceclofenac and duration of release of the both Aceclofenac and Rabeprazole drug was enhanced compared to pure drug formulation.

REFERENCES

[1] Şeyda Akkuş Arslan and Figen Tirnaksiz. *Aceclofenac. J. Pharm. Sci*., **2010**, *35*, 105-118.
[2] Aulton ME. Pharmaceutics: The Science of Dosage Form Design. International Student Edition: 304-321, 347-668.
[3]B. Apparao. *International Journal of Pharmaceutical Sciences and Drug Research* **2010**, 2(2): 146-150-146.
[4] Shobhit Kumar; Satish Kumar Gupta and Pramod Kumar Sharma. *Asian Journal of Pharmacy and Life Science*. **2011**, 1 (4): 396-400.
[5]S. Kumar ;R. Malviya ;P.K Sharma. Solid Dispersion: *Afr. J. Basic. Appl. Sci*. **2011**, 3:116-125.
[6]K. Gowthamarajan.. *International Journal of PharmTech Research*, **2010**, 2(4):2347-2356.
[7]B. Ramana. *Scholars Academic Journal of Pharmacy*, **2013,** 2(2):113-118.
[8]Santosh Ghosh and B.B Barik. *Tropical Journal of Pharmaceutical Research*, 2010, 9 (3): 265-273.
[9] Arjun Sharma. *International Journal of Drug Development & Research.* **2011,** 3(1): 307-313.
[10] Umesh.D .Shivhare; Nandkishor D.Adhao; Dr.Kishore.P.Bhusari; Dr.Vijay.B. Mathur and Mr.Digvijay U. Ambulkar. *International Journal of Pharmacy and Pharmaceutical Sciences*. **2009**, (2), 74-80.
[11] A. Badoni .*The Pharma Innovation.*, **2012**, 1(8): 50-58.
[12] R. Shah; C. Magdum; S.K Patil; D. K Chougule and N. Naikwade. *Research J Pharm and Tech*. **2008**, 1(4): 430- 432.
[13] Dinanath Gaikwad; Jadhav R.T; Amol Limkar; Sangeeta S; Kisan Bobe; Manoj Patil; Trushali Khade; Bhaskar Gavitre; Vivek Kulkarni and Uday Gaikwad. *International Journal* of *Research in Pharmaceutical and Biomedical Sciences*. **2011,** 2 (1):310-318.
[14]Nazim Saikh *Int J Pharm Sci.* **2011**, 3(2): 145-148.
[15]G Sridhar Babu; D Vijay Kumar1; Ch Jyothi1; P S Malathy and H Ramana. *International Journal of Pharmaceutical Research and Biomedical Analysis.* **2014,** 2(3): 11-21.
[16]S. Chakraborty; S. Sarkar; and S.K. Debnath. *International Journal of Chem Tech Research*, Vol.1, **2009**, 663-666.
[17]Garcia, C. V., Paim, C. S., Steppe, M., Elfrides E.S. *Journal of Pharmaceutical and Biomedical Analysis.* **2006,** 46:833–837.
[18]P. Suresh Kumar; S. Navaneetha Krishnan; S. Pavani; Y. Surendarnath; S. Divya and Y. Sahithi , *Scholars Research Library***, 2012**, 4 (1): 287-295.
[19]KL. Senthilkumar; M. Muthukumaran and B. Chenchuratnam. *International Journal of Advances in Pharmacy, Biology and Chemistry***. 2012,** 1(1): 8-14.
[20]T. Parashar. *International Journal of Research and Development in Pharmacy and Life Sciences.* **2013,** 2(2):262-269.
[21] Santosh Patel. *International Journal of Pharmacy and Pharmaceutical Sciences*. **2010,** 2(3): 144-156..
[22] H.S. Patil. *International Journal of Pharmaceutical, Chemical and Biological Sciences*. **2014**, 4(3): 470-478.
[23] B.Rama; Shalem Raju Talluri and Grace Rathnam. *Journal of Pharmacy and Biological Sciences***. 2014**, 9(5):14-20.
[24] Janhavi R Rao; Vishal V Bharekar; Toufik S Mulla; Savita S Yadav and Milind P Rajput. *International Journal of Chemtech Research Coden***. 2012**, 4(4): 1595 -1600.