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Evaluation Of Various Dissolution Parameters On Aceclofenac Sustained Release Tablets

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Abstract:

The present studies were designed to investigate the evaluation of various dissolution parameters on aceclofenac sustained release tablets.The marketed products of aceclofenac tablets were taken. The rate of release of from Aceclofenac the Sustained release tablets was determined using a USP Dissolution Testing Apparatus. The dissolution test was carried out using 900ml of dissolution medium at 37 ± 0.5^0 at three rotational speeds 1) 50 rpm 2)75 rpm and 3) 100rpm to study the effect of rotational speed on release .Dissolution media viz,(1) simulated gastric fluid of pH 1.2,(2) Phosphate buffer of pH 6.8, and (3) Phosphate buffer of pH 7.4 were used in order to study the effect if pH on release of Aceclofenac. The effect of type of dissolution apparatus i.e. Type I (Basket type) and Type II (Paddle type) was studied. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at the end of 1,2,3,4,5,6,7,8,9, and 10 hours and the withdrawn volume was replaced with fresh dissolution media. The samples were filtered through a 0.45µ membrane filter. Absorbance of these solutions was measure at 275 nm using a Shimadzu UV - 1601 UV / Visible double beam spectrophotometer. Cumulative percent drug release was calculated using an equation obtained from the standard curve. Results indicated that only one of three brands gave pH independent drug release.In general, all the brands followed the diffusion mechanism of drug release.% Drug released can be increased by using Paddle type apparatus.As per Standard Procedure PBS(6.8) is essential for maximum release of drug.

Introduction:

The in *Vitro* dissolution test is an analytical tool used for the verification of drug release processes and formulation selection within the pharmaceutical industry[(1)].In *vitro* dissolution testing is a reliable index to predict the in *vivo* performance accurately. In order to validate the in *vivo* performance of the preparations, it is essential to test the preparation on human volunteers, however costly and tedious the method is. Furthermore, it is not practical to conduct human studies of similar preparations.[(2,3,4)]

Aceclofenac(2-[[2-[2-[-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetic acid) is an orally administered phenyl acetic acid derivatives with effects on a variety of inflammatory mediators widely use as an Analgesic & Anti-inflammatory.

It is a white or almost white crystalline powder.Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose. The drug is highly protein bound (7.99%).70-80% drug is excreted through renal clearance in urine and 20% is

excreted through faeces. Biological Half life is 4 hours.Soluble in methanol acetone and DMSO.Store in a well closed container and keep in dry place and away from sunshine.e, efforts are taken to develop modified release, once / twice-a-day formulations. Hence in this study an attempt is made to study the effects of various dissolution test parameters such as apparatus type, rotation speed and type of dissolution medium (pH of the medium) on the dissolution rate of commercially available sustained release Aceclofenac tablets.[5,6,7]

Dissolution is a process in which a solid substance solubilize in given solvent i.e. mass transfer from the solid surface to the liquid phase. Several theories to explain to drug dissolution have been proposed, some of important are:-

(1) Diffusion - layer model/film therory.
(2) Danckwerts model / penetration / surface renewal theory.
(3) Interfacial barrier model/ double barrier/ limited theory.[9]

The objectives of this investigation was to determine the effects of various dissolution test parameters such as apparatus type, rotational speed and type of dissolution medium (pH of the medium) on the dissolution rate of Aceclofenac. The parameters were evaluated using commercially available Sustained release tablets of Aceclofenac.

Materials and Methods:

Aceclofenac (Puredrug), the commercial brands of Aceclofenac (Hifenac, Acene,Movig SR 200 mg), Sustained Release tablets (each containing 200 mg of Aceclofenac) were coded as B1,B2 and B3 respectively. All the reagents used were of Analytical grade.

Product Characterization

The tablets were physically characterized for average weight, hardness, friability, size and shape. They were also evaluated for content uniformity.

Evaluation of Effect of Dissolution Parameters

The rate of release of from Aceclofenac the Sustained release tablets was determined using a USP Dissolution Testing Apparatus. The dissolution test was carried out using 900ml of dissolution medium at 37 ± 0.5^0 at three rotational speeds 1) 50 rpm 2)75 rpm and 3) 100rpm to study the effect of rotational speed on release .Dissolution media viz,(1) simulated gastric fluid of pH 1.2,(2) Phosphate buffer of pH 6.8, and (3) Phosphate buffer of pH 7.4 were used in order to study the effect if pH on release of Aceclofenac. The effect of type of dissolution apparatus i.e. type I (Basket type) and type II (Paddle type) was studied. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at the end of 1,2,3,4,5,6,7,8,9 and 10 hours and the withdrawn volume was replaced with fresh dissolution media. The samples were filtered through a 0.45µ membrane filter. Absorbance of these solutions was measure at 275 nm using a Shimadzu UV - 1601 UV / Visible double beam spectrophotometer. Cumulative percent drug release was calculated using an equation obtained from the standard curve.

Experimental work :

Preparation of calibration curve in 0.1 N HCL :

- Prepare 0.1 N HCL is prepared by diluting 8.5ml in one litre
- Dissolve 10mg drug in methanol, pipette out 1 ml and dilute upto 100ml than make the 1,2,3,4,5,6,7,8,9 µg/ml, than take the calibration curve in UV-spectrophotometer.

Preparation of calibration curve in Phosphate buffer 6.8 :

- Prepare phosphate buffer 6.8 by dissolving potassium dihydrogen ortho phosphate in 200ml and 0.8 gm NaOH (22.4 ml) in 50ml distill water, than mix both and dilute upto one litre.
- Now take the calibration curve of the phosphate buffer 6.8 same as that of 0.1N HCL.

Preparation of calibration curve in Phosphate buffer 7.4 :

- Prepare phosphate buffer 7.4 by dissolving potassium dihydrogen ortho phosphate in 200ml and 0.8 gm NaOH (39.1 ml) in 50ml distill water, than mix both and dilute upto one litre.
- Now take the calibration curve of the phosphate buffer 6.8 same as that of 0.1N HCL.

Evaluation of Tablet :

1. Thickness :

The thickness of the tablets was determined using a thick-ness gauge. Ten tablets from each brand were used, and average values were calculated.

2. Weight Variation :

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official methods described in Indian pharmacopoeia.

3. Drug content :

Dissolve 0.3gm in 40ml of methanol and titrate it with 0.1M NaOH determined its end point potentiometrically. 1 ml of 0.1M NaOH is equivalent to 35.42mg of $C_{16}H_{13}CL_2NO_4$

4. Hardness and Friability :

The hardness and friability of 20 tablets of each brand were determined using the Monsanto hardness tester and the 10 tablets of each brand were determined using the Roche friabilator respectvely.

5. *IN-VITRO* dissolution study :

The *in vitro* dissolution study was carried out using USP Type 2 dissolution apparatus. The study was carried out in 900ml of 2% SLS in0.1N HCL for first 2 hours and then 900ml of phosphate buffer (pH 6.8) from 3 to 24 h. The dissolution medium was kept in Thermostatically controlled water bath, maintained at 37 ± 0.5^{o} C**.** The paddle was lowered so that the lower end of the stirrer was 275mm above from the base of the beaker. The pre-weighed tablate was then introduced into the dissolution jar and the paddle was rotated at 75 rpm. At different time intervals, 5ml sample was withdrawn and analyzed spectrophotometrically at 275mm for the drug release. At each time of withdrawal,5 ml of fresh corresponding medium was replaced into the dissolution flask.

Result and Discussion:

. The Commercial Aceclofenac Sustained release tablets (B1 to B3) showed an average weight ranging from 340 to 360 mg. All the brands showed uniform hardness and friability values, were caplets and showed uniform drug content.

Effect of Different Dissolution Medium on Aceclofenac Sustained Release Tablets: Brand B2 showed pH independent release while brand B1 and B3 showed a pH dependent release, such that the release increased with increase in pH. The ionized Aceclofenac has a tendency to be absorbed to the negatively charged intestinal epithelium affecting the drug absorption pattern. Thus the absorption window of Aceclofenac is predominantly in the small intestine and follows a saturable dose dependent mechanism. Hence the sustained release matrix is designed to produce pH dependent release in case of brand B1 and B3.

Table: Dissolution Profiles of Aceclofenac Sustained Release Tables in Different Dissolution Medium.

Media	%Drug release		
	Brand B1	Brand B2	Brand B3
0.1 N HCl media	51.08	53.52	51.23
PBS(Ph-6.8)	89.9	87.03	86.92
PBS(Ph-7.4)	93.03	83.02	90.78

Effect of Agitation Speed on Release of Aceclofenac Sustained Release Tablets:

For this parameter the dissolution test was conducted at three different rotational speed 50 rpm, 75 rpm and 100 rpm using 0.1 NHCl(1^{st} 2 hr) & PBS(pH 6.8) as the dissolution medium. No significant difference was observed in the release of Aceclofenac on varying the agitation speed from 50 to 100 rpm. This indicates that the matrix follows diffusion type of release mechanism.

Agitation speed	% Drug release
50 rpm	88.5
75 rpm	89.9
100 rpm	88.02

Effect of Type of Dissolution Apparatus on Release of Aceclofenac Sustained Release Tablets:

The dissolution profile from the sustained release tablets was generated using USP dissolution apparatus XXIV Type I (Basket type) and Type II (Paddle type) to study the effect of hydrodynamics on the release profile. The dissolution profile was conducted in 0.1NHCl(1^{st}2hr) & PBS(pH6.8) at 75 rpm for both the apparatus using brand B1 as the sample for Aceclofenac Sustained release tablets. The release profile obtained by using Type II (Paddle type) was much higher in comparison to that obtained by using Type I (Basket type).

That can be attributed to the fact that the surface area of the tablets exposed is more in case of USP type II since the tablet is placed in the jar and all the surface of the tablets are free through which release of occures. Use of sinkers may minimize this problem but sinkers as such restrict the swelling of the diffusion matrix there by hindering the release mechanism. Hence although USP Type II is recommended for dissolution testing of Tablets in European and US pharmacopoeias, taking into account the corresponding hydrodynamics use of USP Type II (Paddle type) gives a complete release in case of diffusion type sustained release matrixes.

Apparatus type	% Drug release
Basket type	83.82
Paddle type	89.9

Conclusion

Results indicated that only one of three brands gave pH independent drug release.In general, all the brands followed the diffusion mechanism of drug release.
% Drug released can be increased by using Paddle type apparatus.As per Standard Procedure PBS(6.8) is essential for maximum release of drug.

Acknowledgement:

Heartful thanks to SURYADRUGS & PHARMACEUTICS,ANKLESHWAR,My guide Prof. J. J. Chudasma,and My Principal Dr.P. Bose.

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Figures:

Fig:1 Calibration curve of Aceclofenac in 0.1 N HCl

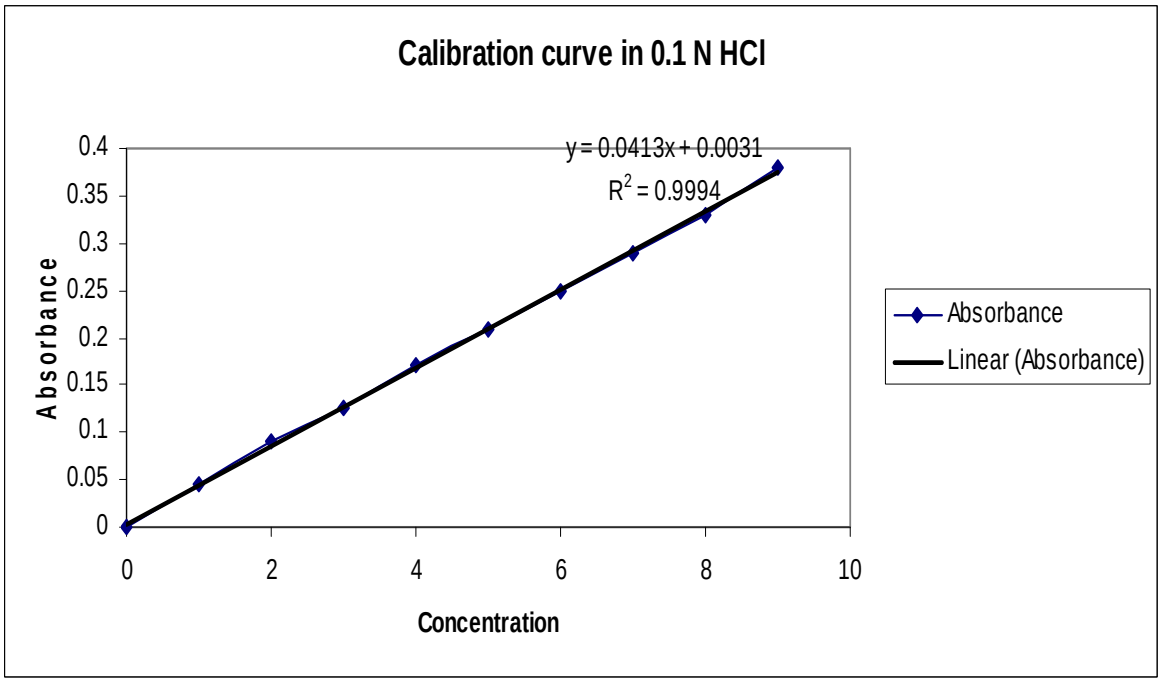


Figure 2: Calibration curve of aceclofenac in PBS (pH 6.8)

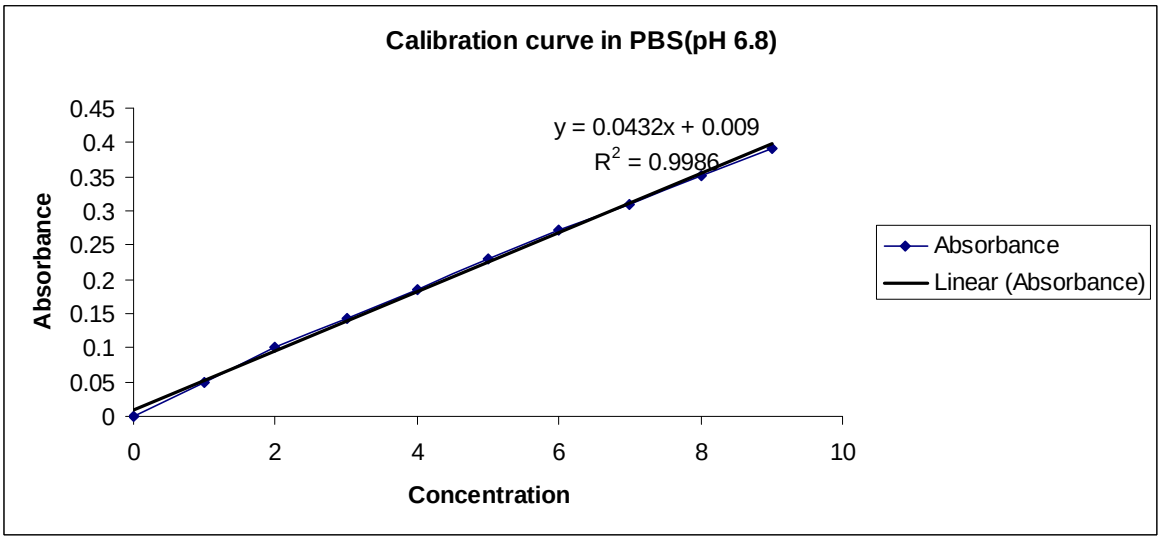


Figure:3 Calibration curve of Aceclofenac in PBS (pH 7.4)

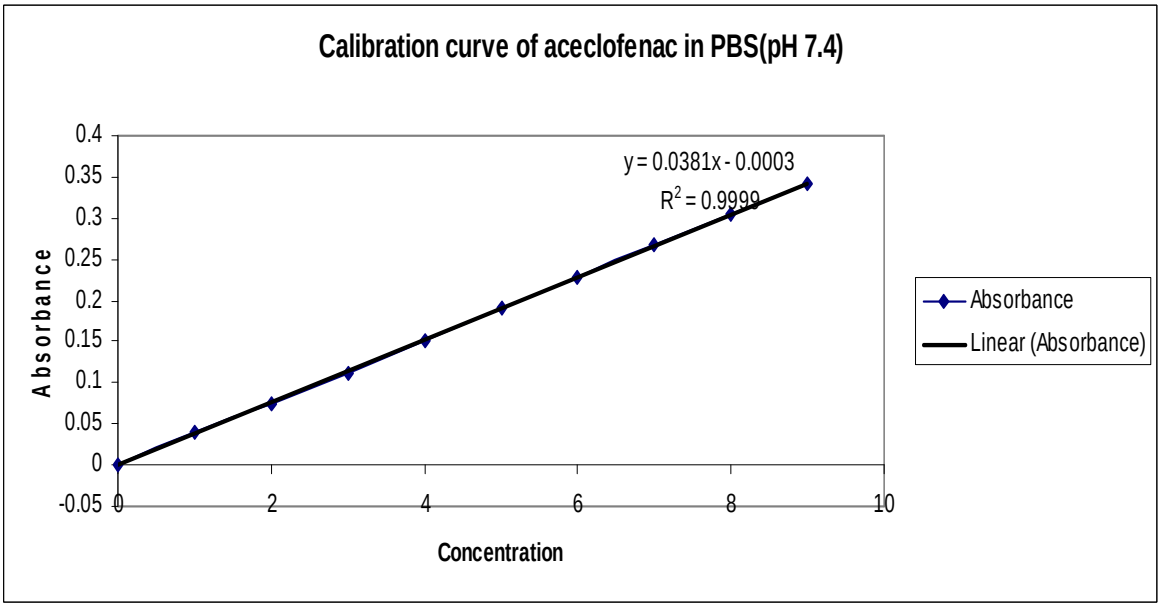


Fig:4 % Drug released in different dissolution medium

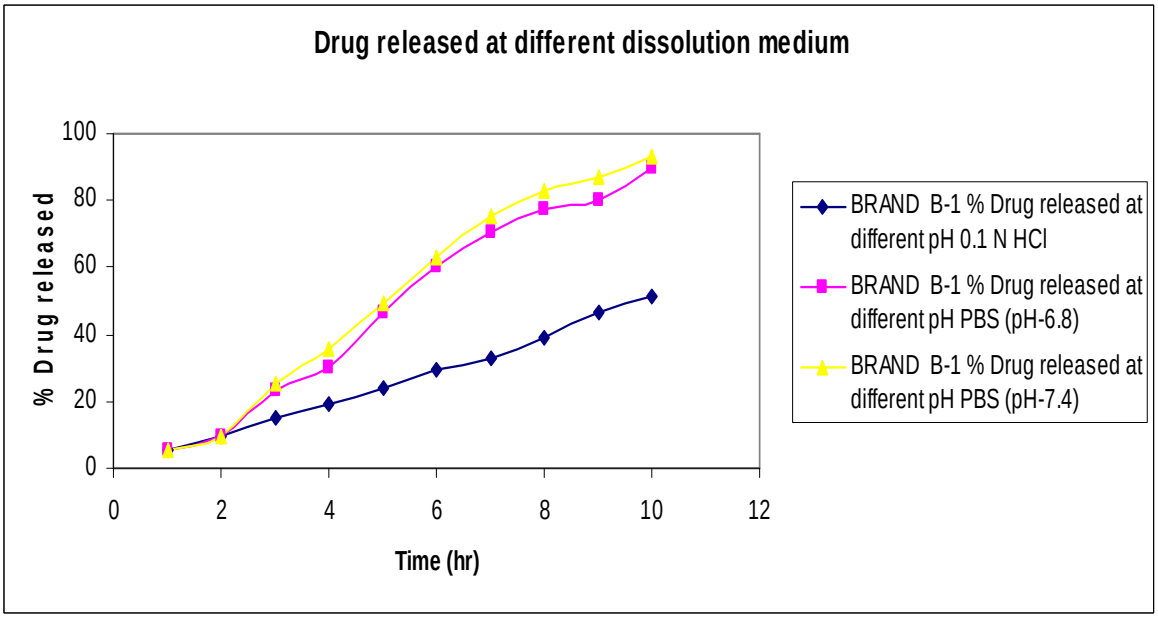


Fig:5 % Drug released in different dissolution medium

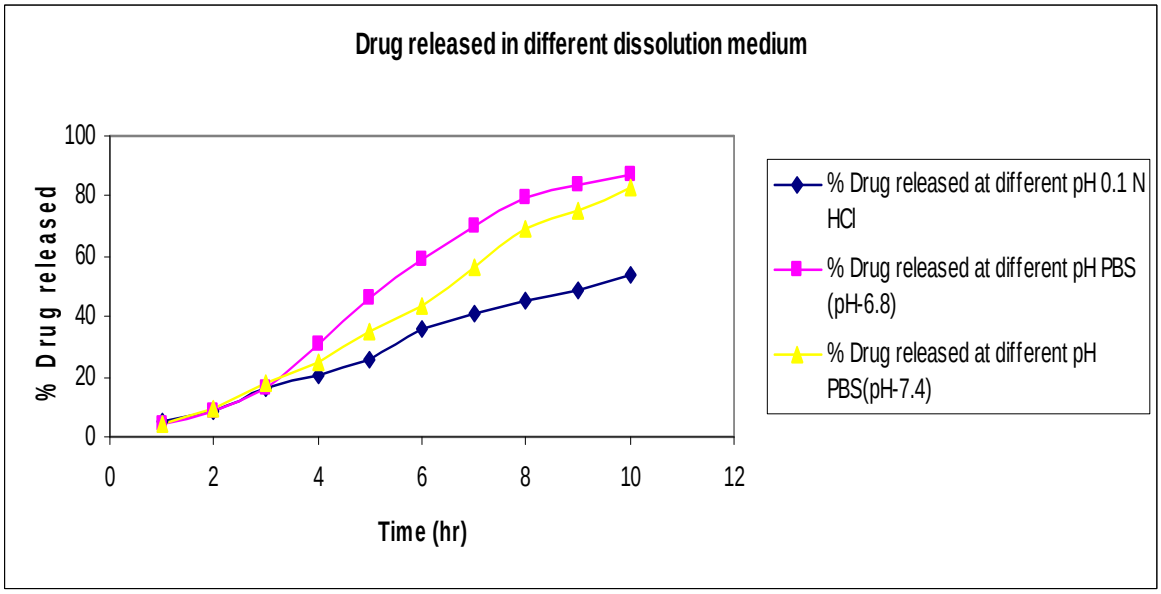


Fig:6 % Drug released in different dissolution medium

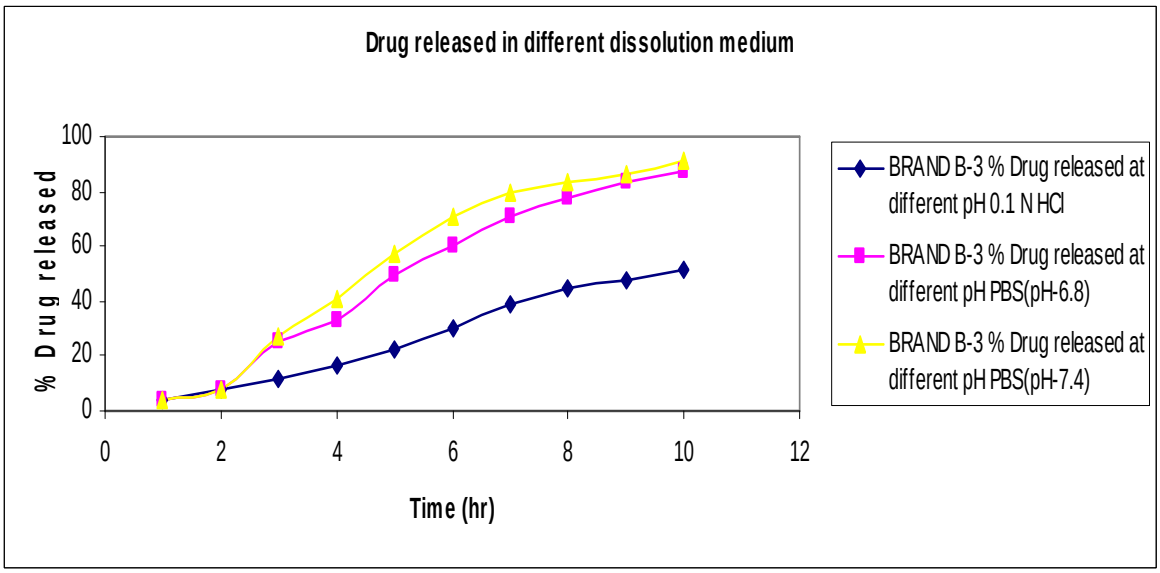


Fig: 7 Dissolution Profiles of Aceclofenac Sustained Release Tables in Different Dissolution Medium.

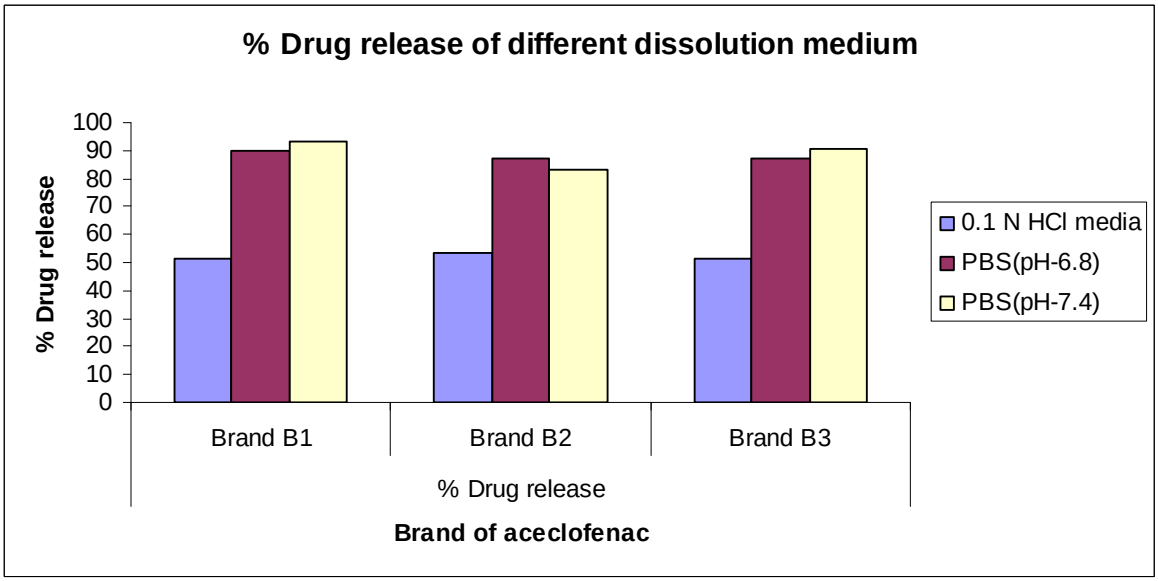


Fig:8 % Drug released at different agitation speed

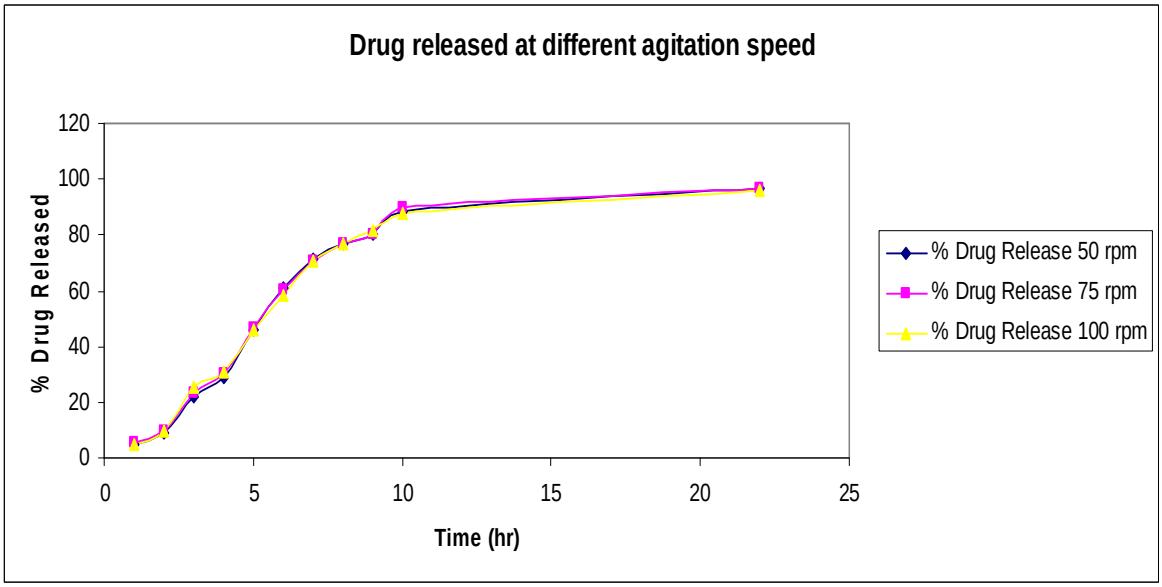
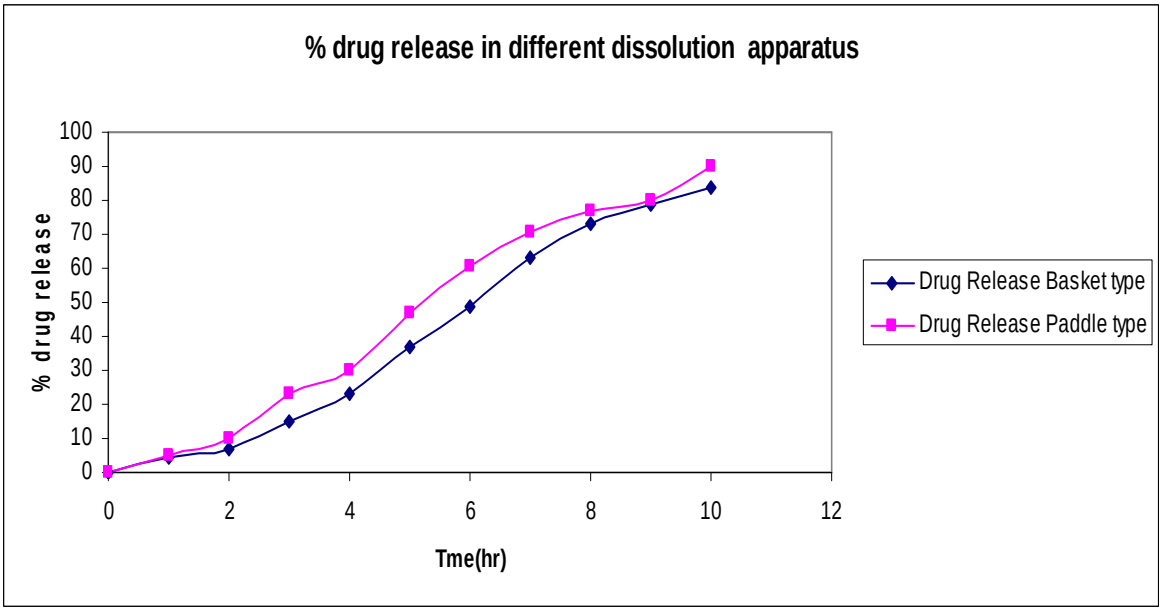


Fig:9 % Drug released in different dissolution apparatus



Tables:

Table : 1 Calibration curve of aceclofenac in 0.1N HCL

Concentration(µg/ml)	Absorbance
0	0
1	0.046
2	0.09
3	0.125
4	0.17
5	0.21
6	0.25
7	0.289
8	0.33
9	0.38

Table : 2 Calibration curve of aceclofenac in PBS (pH-6.8)

Concentration((µg /ml)	Absorbance
0	0
1	0.05
2	0.1
3	0.143
4	0.184
5	0.23
6	0.272
7	0.31
8	0.352
9	0.392

Table : 3 Calibration curve of Aceclofenac in PBS (pH-7.4)

Concentration(µg/ml)	Absorbance
0	0
1	0.04
2	0.075
3	0.112
4	0.151
5	0.19
6	0.228
7	0.267
8	0.3043
9	0.3425

Table 4:Evaluation of Tablets

PARAMETER	BRAND B1	BRAND B2	BRAND B3
Weight (mg)	350±5%	350±5%	350±5%
Drug content	97.0	97.89	97.46
Thickness(mm)	4.20±0.2 mm	4.25± 0.3mm	4.12± 0.1 mm
Hardness	10kg/cm^2	12kg/cm^2	13 kg/cm^2
Friability (%)	0.02%	0.01%	0.03%

Table:5 % Drug released in different dissolution medium

BRAND B-1			
Time(hr)	% Drug release at different Ph		
	0.1 N HCl	PBS (pH-6.8)	PBS (Ph-7.4)
1	5.2	5.2	5.3
2	9.8	9.8	9.6
3	14.9	23.3	25.6
4	18.89	29.89	35.89
5	24.3	46.8	49.08
6	29.5	60.6	63.02
7	32.6	70.8	75,09
8	38.9	77.08	83.02
9	46.8	80.02	87.02
10	51.08	89.8	93.03

Table:6 % Drug released in different dissolution medium

BRAND B-2			
Time(hr)	% Drug released at different pH		
	0.1NHCl	PBS(6.8)	PBS(7.4)
1	4.77	4.32	4.35
2	8.8	8.6	9.02
3	15.9	16.34	18.04
4	20.9	30.49	25.04
5	25.6	46.39	35.05
6	35.75	58.55	43.34
7	40.89	70.45	56.04
8	45.02	79.24	69.04
9	49.07	84.02	75.06
10	53.52	87.03	83.02

Table:7 % Drug released in different dissolution medium

BRAND B3			
Time(hr)	% Drug released at different pH		
	0.1NHCl	PBS(6.8)	PBS(7.4)
1	3.4	3.94	3.6
2	8.08	8.03	7.98
3	12.03	25.32	27.62
4	16.4	33.43	40.56
5	22.03	49.46	57.39
6	30.05	60.33	70.4
7	38.49	70.43	79.45
8	44.77	77.29	83.08
9	47.83	83.24	86.02
10	51.23	86.92	90.78

Table: 8 Dissolution Profiles of Aceclofenac Sustained Release Tables in Different Dissolution Medium.

Media	%Drug release		
	Brand B1	Brand B2	Brand B3
0.1 N HCl media	51.08	53.52	51.23
PBS(Ph-6.8)	89.9	87.03	86.92
PBS(Ph-7.4)	93.03	83.02	90.78

Table:9 % Drug released at different agitation speed

Time(hr)	% Drug release at different agitation speed		
	50 rpm	75 rpm	100 rpm
1	4.9	5.2	4.77
2	9.1	9.8	9.5
3	22.08	23.3	25.3
4	28.99	29.89	30.89
5	46.2	46.8	45.8
6	60.8	60.6	58.6
7	71.02	70.8	70.8
8	76.89	77.08	76.54
9	80.55	80.02	81.88
10	88.5	89.9	88.02
22	96.55	96.93	96.08

Table:10 % Drug released in different dissolution apparatus

Time(hr)	Basket type	Paddle type
0	0	0
1	4.54	5.2
2	6.78	9.8
3	14.78	23.3
4	23.11	29.89
5	37.01	46.8
6	49.02	60.6
7	63.23	70.8
8	73.02	77.08
9	79.02	80.02
10	83.82	89.9
22	93.82	96.93