International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 882-890 www.ijprajournal.com ISSN: 2456-4494

Formulation Development and Evaluation of Baclofen HCL Based on Hydrodynamically Drug Delivery System

Rajnikant, Dr.Saurabh Sharma, Ajeet Kumar
Research Scholar, Vivek College of Technical Education Bijnor U.P (246762)
Principal, Vivek College of Technical Education Bijnor U.P (246762)
Professor,Vivek College of TechnicalEducationBijnor U.P

Submitted: 15-11-2022 Accepted: 26-11-2022

ABSTRACT:
Dosage forms that can be retained in the stomach for prolonged and predictable period of time are called gastro-retentive drug delivery systems (GRDDS). The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance.

KEYWORDS: -Potentially, Bioavailability, Retention Hydro Dynamically, Baclofen Hydrochloride.

I. INTRODUCTION:

The oral route represents nowadays the predominant and most preferable route for drug delivery. Unlike the majority of parenteral dosage forms, it allows ease of administration by the patient and it's the natural, and there for a highly convenient way for substances to be introduced in to the human body. Oral drug delivery systems (DDS) are mainly immediate release (conventional) drug delivery systems which are intended to disintegrate rapidly, and exhibit instant drug release. They are associated with a fast increase and decrease, and hence fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side effects. Administration of the DDS several times per day therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion leading to poor patient compliance. In order to overcome the drawbacks associated with conventional drug delivery systems, several technical advancements have led to the development of Modified release systems that could revolutionize method of medication and provide a number of therapeutic benefits. Modified release systems, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance (reducing the frequency of dosing), as well as reducing the side effects.

Using current release technology, oral delivery for 24 hours is possible for many drugs but the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion, to ensure continuous absorption of the released drug. A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Such drugs are said to have an absorption window i.e., absorbed only from specific areas of the GIT, principally due to their low Permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, as well as to the degradation of the drug by the microorganisms present in the colon.

Dosage forms that can be retained in the stomach for prolonged and predictable period of time are called gastro-retentive drug delivery systems (GRDDS).The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. [8] Floating systems, first described by Davis in 1968 are low-density systems that have a density of less than1g/ml, to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 882-890 www.ijprajournal.com ISSN: 2456-4494

II. MATERIAL AND METHODS:

Table1: All ingredients with their source.

S.No.	Materials	Source
1	Baclofen	Gift sample from Natco pharma Ltd.,Hyderabad
2	HPMC K4M	Colorcon Asia PvtLtd.,Goa
3	HPMC K15M	-
4	HPMC K100M	-
5	Xanthan gum	LobaChemie Pvt. Ltd., Mumbai
6	Guar gum	-
7	PEO WSR-301	ColorconAsiaPvt Ltd.,Goa
8	PEO WSR-303	-
9	Sodium bicarbonate	S.D. Fine chemicals Ltd., Mumbai
10	Avicel PH-102	Signet chemical corporation, Mumbai
11	Talc	S.D. Fine chemicals Ltd., Mumbai
12	Magnesium stearate	-
13	Hydrochloric acid	Loba Chemie Pvt. Ltd., Mumbai

Preformulation studies:

Organoleptic evaluation:

Organoleptic characters like color, odor, and taste of drug were observed and recorded using descriptive terminology.

Development of analytical method:

A survey of literature reveals that few analytical methods such as HPLC, UV/VIS spectrophotometric method were reported for the estimation of Baclofen in formulation. A simple economical, convenient, reproducible and precise UV spectrophotometer method was employed for the assay as well as for the in-vitro dissolution studies.

UV Spectroscopy:

Preparation of Stock solution:

50mg of the drug (BCF) was accurately weighed and transferred to the 50mL volumetric flask. It was dissolved in sufficient quantity of 0.1NHCl and volume was made up to the mark with 0.1NHCl to obtain a stock solution of 1000µg/ml.

Determination of UV Absorption Maxima (λ max) of Baclofen in 0.1NHCl:

From the stock solution, 50µ L was transferred to a 5mL volumetric flask and the volume was made up to the mark with 0.1NHCl. The resulting solution containing 10µg/ml. BCF in 0.1NHCl was scanned from 200-400 nm in 0.1NHCl as a blank using double beam UV/VIS spectrophotometer. The wavelength maximum was found to be at 220 nm.

Determination of micrometric properties of the powder blends:

The following tests were performed in-order to determine the flow properties of the powder blends.

Bulk Density:

Bulk density is of great importance when one considers the size of a high-dose drug product or homogeneity of a low-dose formulation. The homogeneity of a low-dose formulation in which there are large differences in drug and excipients could lead to segregation.

Apparent Bulk density (g/ml) was determined by pouring (pre-sieved 18-mesh) gently 10g of the sample through a glass funnel into a 50mL graduated cylinder. Then after pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the Graduation marks on the cylinder. The volume measure was called as the bulk volume and the bulk density was calculated following formula.

Bulk density = Weight of powder / Bulk

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 882-890 www.ijprajournal.com ISSN: 2456-4494

Tapped Density:

Tapped density (g/ml) was determined by pouring gently 10g of sample through a glass funnel into a 50Ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained (100 taps). Volume occupied by the sample after tapping was recorded as the tapped volume (ml) and tapped density was calculated from the following formula.

Tapped density = Weight of powder / Tapped volume

Carr's Compressibility Index(%):

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. High density powder stands to possess free flowing properties. A useful empirical guide is given by the Carr's index or compressibility
index calculated from bulk density and tapped density.

Compressibility index=1-100

Where,
V= volume of powder blend before tapping V0 = volume of powder blend after 100 tapping's

Hausner's ratio:

Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A low value indicates better flow and vice versa.

Hausner's ratio=Tapped density/Bulk density

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. Angle of repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure of the flow ability of powder/granules. Angle of repose was calculated using the following formula.

$$\theta = \tan^{-1}$$

Where,
θ = Angle of repose
h = Height of the powder cone r =Radius of the powder cone.

The specifications for flow characteristics of powders are given in Table 2

Table2:Specifications for flow characteristics of powders

S.NO	TYPEOFFLOW	ANGLEOF REPOSE (°)	COMPRESSIBILITY INDEX(%)	HAUSNER'S RATIO
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair(aidnot needed)	36-40	16-20	1.19-1.25
4.	Passable (Mayhangup)	41-45	21-25	1.26-1.34
5.	Poor(mustagitate,vibrate	46-55	26-31	1.35-1.45
6.	Verypoor	56-65	32-37	1.46-1.59
7.	Very poor	>66	>38	>1.6

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 882-890 www.ijprajournal.com ISSN: 2456-4494

Formulation of Baclofen SR floating matrix tablets:

Table 3: Formulae of floating matrix tablets of BCF

Ingredients(%w/wof200mgtablet)	F1	F2	F3
BCF	11.5	11.5	11.5
HPMCK100M	30	40	20
HPMCK15M	—	—	—
HPMCK4M	—	—	—
Sodium bicarbonate	25	25	10
AvicelPH-102	31.5	21.5	56.5
Talc	1	1	1
Magnesium stearate	1	1	1
Total	100	100	100

Procedure for the preparation of tablets:

BCF and all other ingredients were individually passed through sieve no≠60. Accurately weighed quantities of drug, polymer, sodium bicarbonate, MCC were transferred to a polythene bag and mixed homogenously for 15 minutes. The powder mix was then lubricated with talc and magnesium stearate. The powder blend was compressed in to tablets on a single punch tablet machine using 8mm flat round punches.

Evaluation Parameters of Post-compression Tablet:

Hardness: The hardness of the tablets was measured with a Monsanto hardness tester. The results reported were mean and standard deviation of 3 tablets for each formulation and expressed in kg/cm2. Oral compressed tablets normally have a hardness of 4-9 kg/cm2.

Friability (%F):

20 tablets from each batch were selected randomly and weighed. These pre-weighed tablets were subjected to friability testing using Roche friabilator for 100 revolutions. The tablets were subjected to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de- dusted and weighed again. Following formula was used to calculate the friability%.

$$\%F = 1 - (\text{Final weight} / \text{Initial weight}) 100$$

A maximum weight loss of not more than 1% of the tablet weight during the friability test is generally considered acceptable.

Weight variation:

20 tablets were randomly selected from each batch, weighed individually. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test if the weights of not more than 2 of tablets differ by more than the percentage listed in Table 4.
And no tablets differ in weight by more than double that percentage.

Table 4: Weight variation allowed for uncoated tablets.

Average weight of tablet (mg)	Percentage difference allowed
≤ 130	10
130-324	7.5
>324	5

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 882-890 www.ijprajournal.com ISSN: 2456-4494

Drug content uniformity:

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. Accurately weighed powder sample (200mg) equivalent to 23mg of BCF was transferred to a 100mL volumetric flask, and made up to volume 0.1NHCl. The contents of the volumetric flask were sonicated for 15 minutes in order to extract the drug into 0.1NHCl. The solution was then filtered, suitably diluted with 0.1NHCl and the absorbance was measured at 220nm. The estimations were carried out in triplicate and the results are given in Table 5.

Table5: Post-Compression Parameters of BCF floating tablets.

Formulations	Avg.wt(mg) Mean±S.D	Hardness (kg/cm^2)	Friability(%wt.loss)	Drug Content (%)
F1	197±1.3	6.83±0.29	0.46	96.11±0.76
F2	197±1.8	7.0±0.5	0.29	95.89±0.42
F3	198±2.5	4.17±0.29	0.51	98.47±0.83

In-vitro buoyancy Study:

The study involves the determination of the floating lag time and total floating time. Floating lag time is the time required for the tablet to emerge onto the surface of the dissolution medium from the bottom of the dissolution vessel. The duration of floating (total floating time) is the time the dosage form constantly floats on the surface of the dissolution medium (excluding floating lag time).

Procedure:

3 tablets from each batch were transferred to USP XXI type- II dissolution apparatus containing 900mL of 0.1N HCl. The study was performed at the paddle rotational speed of 50 rpm and temperature of 37±0. 5°C.The floating lag time and the total floating time were recorded by visual observation using a stopwatch. The results are given in Table 6.

Table 6: Buoyancy Determinations of BCF floating tablets.

FORMULATIONS	PARAMETERS	
	FLT (SECONDS)	TFT(HOURS)
F1	73.33±15.28	24
F2	210.67±21.01	24
F3	14.67±1.16	24

In-vitro drug release study:

The tablet samples were subjected to in-vitro dissolution study using USP XXI type II (Paddle method) Dissolution rate test apparatus at a temperature of 37+0.5°Cand 50rpm speed. 900mL of 0.1NHCl (pH-1.2)
was used as the dissolution medium. A liquid equal to 5mL was withdrawn at specific time intervals for 24 hours. The dissolution media volume was complimented with fresh and equal volume of blank media (0.1NHCl). The aliquots were filtered and assayed for BCF by measuring the absorbance at 220 nm against
blank (0.1NHCl). The dissolution experiments were carried out in triplicate. The results are given in Tables 6
to 8.

III. RESULT AND DISCUSSION:

Analytical method: Determination of UV Absorption Maxima (λmax) of Baclofen in 0.1N HCl:

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 882-890 www.ijprajournal.com ISSN: 2456-4494

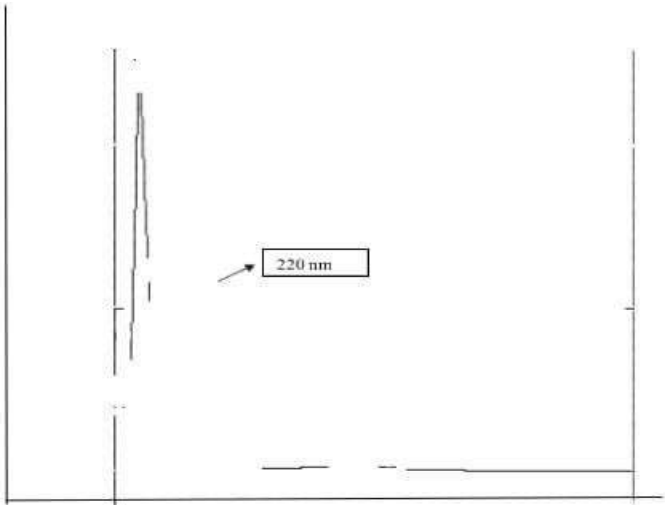

Fig.1 Scanning graph of BCF in 0.1N HCl.

Standard calibration curve of Baclofen in 0.1N HCl (pH-1.2):

Table7: Calibration Curve Data for the Estimation of BCF in 0.1N HCl.

Concentration(µg/ml)	ABSORBANCE(nm)			
	Trial -I	Trial -II	Trial -III	Mean±S.D
2	0.061	0.063	0.05	0.058±0.007
4	0.098	0.106	0.098	0.101±0.005
6	0.155	0.167	0.154	0.159±0.007
8	0.203	0.228	0.195	0.209±0.017
10	0.261	0.279	0.253	0.264±0.013

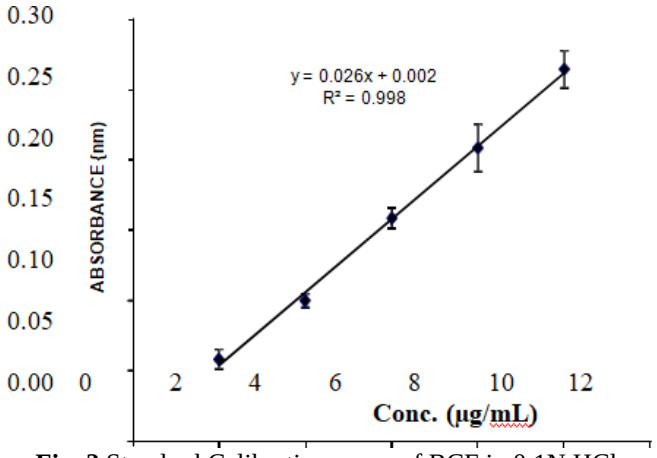

Fig. 2 Standard Calibration curve of BCF in 0.1N HCl.

Solubility Study:

The dissolution medium employed for the gastro-retentive tablets is 0.1NHCl (pH-1.2) (Simulated gastric fluid). Hence, the solubility of Baclofen in 0.1N HCl was determined in order to verify whether sink condition can be maintained in the in-vitro dissolution process employing 0.1N HCl as the dissolution medium. The results of the solubility study are reported in table 9.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 882-890 www.ijprajournal.com ISSN: 2456-4494

Table:8 Solubility Determination of BCF in 0.1N HCl.

MEDIUM	ABSORBANCE (nm)	DILUTIONFACTOR	SOLUBILITY (mg/mL)
0.1NHCl	0.657	100	25.2

FT-IR interpretation:
Reading given in table no7.

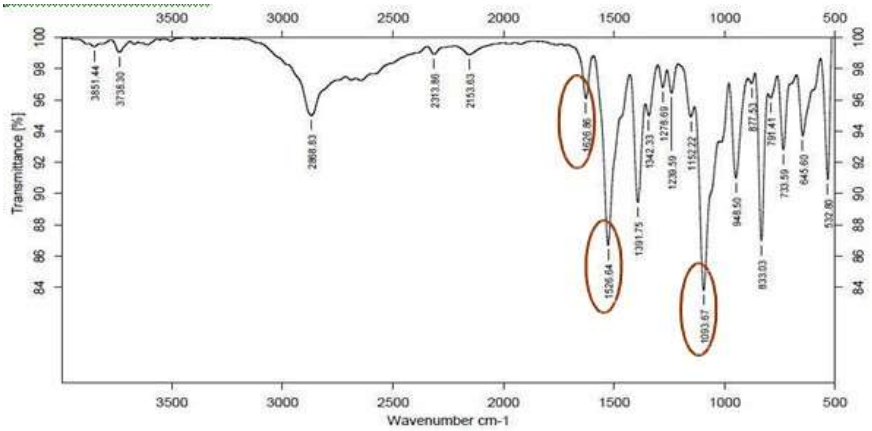

Fig.3 FT-IR Spectrum of BCF.

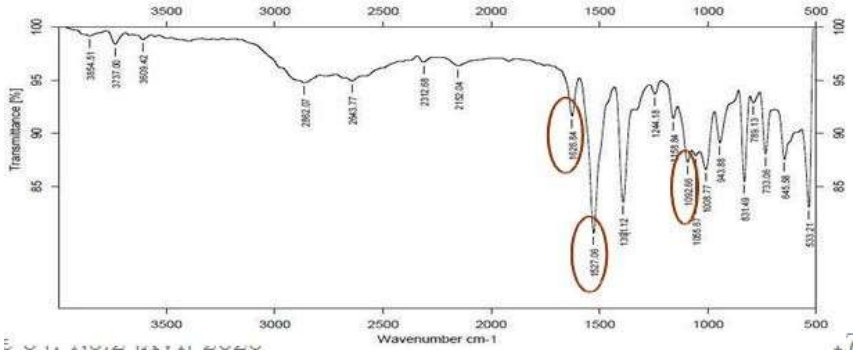

Fig.4 FTIR Spectrum of BCF-HPMC K100M.

Determination of Micromeritics properties of powder blends:

Table: 9 Micromeritic properties of powder blends of various formulations.

Batch code	Angle ofrepose(θ)	Bulk Density(g/mL)	Tapped density(g/mL)	Carr'sindex(%)	Hausner's ratio
F1	34.90	0.222	0.256	13.28	1.15
F2	32.34	0.266	0.310	14.19	1.17
F3	34.54	0.258	0.291	11.30	1.13

Bulk density:
The bulk density of the powder blends ranged between 0.222-0.311 g/mL.

Tapped density:
The tapped density of the powder blends ranged between 0.256-0.356 g/mL.

Carr's compressibility index:
If the compressibility index of the powder blend ranged between 11-15 %, it indicates good flow property. All the blends were within the range (11.11-14.28%), indicating that the blends exhibit good flow property.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 882-890 www.ijprajournal.com ISSN: 2456-4494

Hausner's ratio:
The Hausner's ratio of the powder blends ranged between 1.13-1.17. It indicates good flow property of the blends.

Angle of repose (θ):
The angle of repose for all the powder blends ranged between 31.32°-34.90°, indicating good flow property of the blend.

Drug Release Kinetic Profiles of Formulation F1.

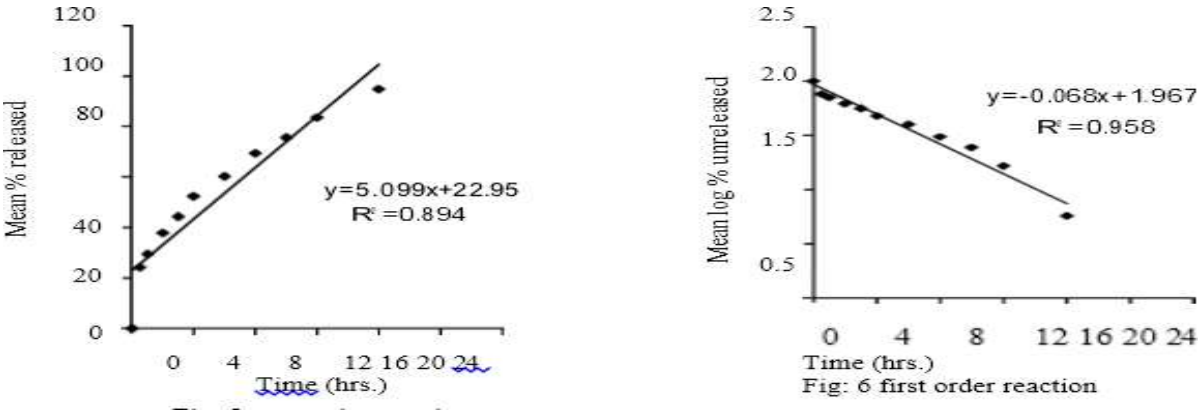

Fig.5 Zero order reaction and first order reaction

The results of the regression analysis are summarized in Table 10.

Table:10 Regression kinetics parameter for Baclofen

Formulation	Zero order		First order		Higuchi		Peppas plot	
	R^2	K0(mg/hr)	R^2	K(hr^{-1})	R^2	KH($mg/hr^{1/2}$)	R^2	n
F1	0.895	5.099	0.959	0.158	0.994	22.713	0.994	0.41
F2	0.843	3.554	0.976	0.119	0.987	19.458	0.992	0.42
F3	0.863	8.339	0.869	0.421	0.989	30.186	0.998	0.33

IV. CONCLUSION:

Finally, once-daily sustained release gastro-retentive floating tablets of Baclofen were successfully formulated in a relatively economical way when compared to the marketed formulation and found to be superior when compared to the marketed formulation.

Spasticity, a condition in which certain muscles are continuously contracted, affects over 12 million worldwide. Generally, spasticity is associated with common neurological disorders like multiple sclerosis, stroke, cerebral palsy and spinal cord injury. Baclofen is the largest prescribed drug for this indication, worldwide. In the market, Baclofen is available as conventional tablets, orally disintegrating tablets and once-daily GRS tablets. Due to short elimination half-life (2.5-4 hours), the conventional and orally disintegrating tablets need to be administered 3-4 times a day (for several days) leading to poor patient compliance and there is also increased incidence of side effects with these formulations. The patient compliance can be improved and the side effects can be minimized with a once-daily sustained release formulation. Absorption of the Baclofen is limited to stomach or upper part of the GI tract i.e, its absorption on arrival to colon (or even before) is low or nonexistent and therefore its bioavailability is incomplete when administered as a sustained release formulation. The bioavailability of the drug can be increased by making the drug completely absorbed in the stomach by gastro-retentive drug delivery system. Even though once-daily extended-release GRS is available in the market (Baclofen OD, INTAS pharmaceuticals), it is very expensive as it is a coated multi-layer gas generating floating tablet. Hence, in the present investigation, efforts were made to develop once- daily sustained release gastro- retentive floating system of Baclofen which is cost effective.

Selection of the optimized formulation and comparison with the marketed formulation:

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 882-890 www.ijprajournal.com ISSN: 2456-4494

Formulation (F3) containing xanthan gum-40%, sodium bicarbonate-12.5% exhibited a very less floating lag time of 20.33±6.03 seconds and total floating time of 24 hours and released 98.47±0.71% of the drug in 24 hours. Hence, it was selected as the optimized formulation. Marketed formulation exhibited FLT of 63.67±4.01 seconds, TFT of 24 hours and released 95.07±0.41% drug in 24 hours. F3 was found to be superior when compared to the marketed formulation.

Determination of Similarity factor:

Similarity factor was calculated and it was found to be 51.60. The similarity factor is within the acceptable limit (>50) which confirms the similarity between the release profiles of F3 and the marketed formulation

REFERENCES:

[1]. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch. Intern. Med. 1990; 150: 1881-1884.

[2]. Getsios D, Caro JJ, Ishak KJ, El-Hadi W, Payne K, O'Connel M, Albrecht D, Feng W, Dubois D. Oxybutynin Extended Release and Tolterodine Immediate Release: A Health Economic Comparison. Clinical Drug Investigation 2004;24:81-88.

[3]. SansomLN.Oralextendedreleaseproducts. Aust.Prescr.1999;22:88-90.

[4]. Basit A, Lacey L. Colonic metabolism of Ranitidine: implications for its delivery and absorption. Int. J. Pharm.2001;227:157-165.

[5]. Baumgartner S, Kristl J, Vrecer F, Vodopivee P, Zorco B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int. J. Pharm.2000;195:125- 135.

[6]. Rocca JG, Omidian H, Shah K. Progresses in Gastro-retentive Drug Delivery System, Business Briefing. Pharm.Tech.:152-156.

[7]. Sood A, Panchagnula R. Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index. Int. J. Pharm.2003;261:27-41.

[8]. Fell JT. Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract.J.Anat.1996;189(3):517-519.

[9]. DavisDW.Method of swallowing a pill.US Patent 3,418,999. December 31,1968.