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Formulation, evaluation and *in vitro* characterization of gastroretentive floating tablet of diclofenac sodium

Muhammad Qaiser Shehzad[1], Taha Nazir[2], Saeed-Ur-Rashid Nazir[1], Nida Taha[3], Tahir Jamil[4] and Muhammad Abdullah Akram[4]

[1]Department of Pharmacy, University of Sargodha, Sargodha, Pakistan
[2]Chemical Pathology & Molecular Biology Research Group, Advanced Multiple Inc., Mississauga ON Canada
[3]Riphah Institute of Pharmaceutical Sciences, Riphah International University (Lahore Campus), Lahore, Pakistan
[4]Department of Pharmaceutics, Facutly of Pharmacy, Gomal University, Dera Ismail Khan, Pakistan

Abstract: Currently a variety of tools and techniques are used to deliver complex medicines. Whereas, certain advanced methods assure the safety and usefulness by regulating the pharmacokinetic and pharmacodynamic. Thus, we aimed this study to develop a novel gastro retentive floating tablets. The formulation was designed to provide the desired controlled and complete release of drug for prolonged period of time. The formulations were evaluated for physical characterization. The obtained results of hardness (4.6-5.1), friability (0.20-0.43%), weight variation (350 ±2 - 350±5) and *in vitro* buoyancy were found within official limits of United Stated Pharmacopoeia (USP). Whereas, the F-7 showed most optimized intra gastric floating characteristics and exhibited 93.87% release of diclofenac sodium in 9 hours. The Floating Lag Time of 8 minutes and Total Floating Time ≥12 hours were recorded. *In-vitro* drug release kinetics evaluated using the linear regression method was found to follow the Zero Order and Peppas model for the release of both the drugs. DSC thermograph and FTIR spectra depicted that there was no chemical incompatibility between drugs and polymers. In conclusion the desgined tablet can be use in clinical practice as model drug. Because, the pre-compression and post-compression parameters were satisfactory and within desired limits.

Keywords: Telmisartan, mouth disintegrating tablet, extended release profile, response surface methodology.

INTRODUCTION

Drug Delivery System (DDS) is the technique or manner of delivering complex drugs to attain a therapeutic effect in human beings or animals. (Yun *et al*, 2015) These are the preparations or devices that permit the introduction of therapeutically active material in the body to increase its safety and usefulness by regulating the degree, place and time of its release into the body. While administering the medicine, the dosage must be wisely calculated so that the body can use the drug. This could be attained by a drug delivery system which permits for precise dosing. (Tiwari *et al*., 2012) Need of drug delivery systems also have to ponder the way in which the drug is metabolized in the body. For specimen, some drugs broken in the GIT and can't be used to administer into the body in such a manner. Others may be hazardous in large quantities; therefore the process of release time should be controlled to deliver medication safely. The usefulness of the drug delivery system is affected, by the interval of time it takes to get a drug to show its therapeutic effect in the body. Effective new approaches of delivery have the capability to decrease the dose and unwanted or undesired effects. (Jain *et al*., 2008).

The idea of FDDS has been discussed in literature in the initial part of 1968, Davis revealed a technique to overcome the trouble confronted by some people in order to silence the voice or blocking during swallowing the tablets. The writer proposed a method that such difficulty can be controlled by offering a grain density of a smaller amount than 1.0g /ml thus the pill will float on the water surface. (Nayak *et al.*, 2010).

Diclofenac sodium is a NSAID (non - steroidal anti-inflammatory drugs). Diclofenac Sodium is a simple vinyl derivative of acetic acid. It looked like a both flurbiprofen and meclofenamate. It decreases fever and inflammation and relieves pain. It is of anthropogenic origin and belongs to the phenyl acetic acid. It belongs to the group of cyclooxygenase (COX) inhibitor on the basis of its mechanism of action. It is also categorized in painkillers and anti-inflammatory medicines. Plasma protein binding of diclofenac sodium is 99%. Renal excretion of diclofenac sodium accounts for 65% and plasma half-life is 1-2 hours. (Alzaher *et al*., 2015). The immediate release tablets of diclofenac sodium which are used to treat the primary dysmenorrhea, mild and moderate pain of rheumatoid arthritis, and arthritis are available**.**

Empirical formula:	$C_{14}H_{10}Cl_2NNaO_2$
IUPAC name:	SODIUM [2-[(2, 6-DICHLOROPHENYL) AMINO] PHENYL] ACETATE
Molecular weight:	318.14

**Corresponding author:* e-mail: taha@advancedmultiple.ca

Anti-inflammatory effects of the Diclofenac are supposed to be due to inhibition of the migration of the leukocyte and inhibition of the enzymes cyclooxygenases (COX-1 and COX-2), it leads to the prostaglandin's synthesis inhibition. It is well absorbed after taking orally. (Taha *et al.*, 2015). Diclofenac Sodium experiences first-pass metabolism; the quantity of drug which enters the circulation is 50 to 60% of the given dose. Peak plasma concentration is typically reached in 1 hour for conventional tablets of Diclofenac sodium, the time to reach peak plasma concentration for delayed release tablets is 2 hours and for extended release tablets the time is 5.25 hours. . Also gets absorbed into systemic circulation by applying topically as a transdermal system or as a gel; plasma concentrations is very low after topical application as compared to when orally administered. (Munjal *et al.*, 2015).

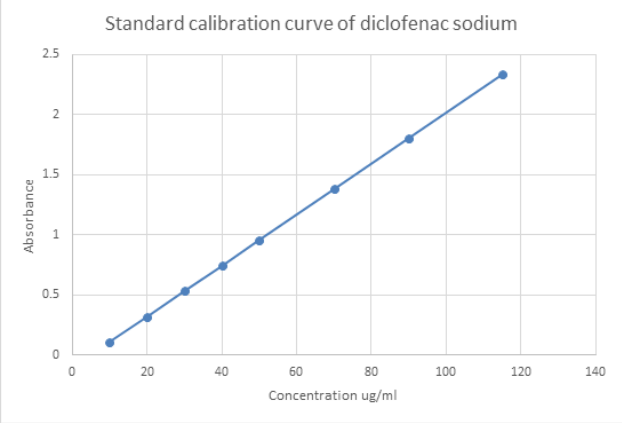

Fig. 1: Standard calibration curve of diclofenac sodium.

After single dose (50-100 mg) provides pain relief for 8 hours. Food can delay the absorption but do not have effect on the degree of absorption. It has wide distribution in animals., its concentrations in synovial fluid may perhaps exceed from the concentration in plasma. Plasma Protein Binding is about 99%. It mainly undergoes liver metabolism through reaction of conjugation and hydroxylation. Some of the metabolites may also display anti-inflammatory activity . 65% of it is excreted in urine and feces and 35% is through bile as metabolites (Singh *et al.*,2012). Oral preparations: 1–2 hours. (Woodhouse & Wyne, 1987).

Moreover, it is well-thought to be faster acting and harmless as compared to ibuprofen. It also has activity for longer time as compared to paracetamol. Diclofenac sodium and potassium are the two salt forms in which diclofenac is mostly used. Diclofenac sodium and potassium have similarity of having same diclofenac base but are different from each other in nature and function, their dose is same even then these cannot be treated as equivalents. Diclofenac potassium is formulated as immediate release, whereas diclofenac sodium is formulated as delayed release. Hence, we aimed this study to formulate, evaluate and *in vitro* characterize the gastroretentive floating tablet of diclofenac sodium.

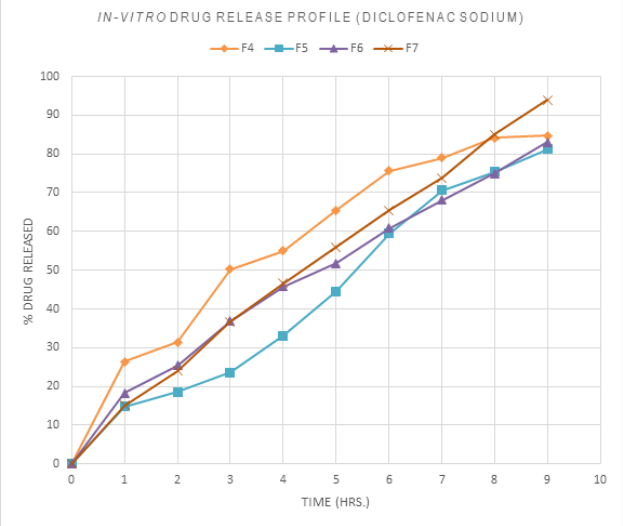

Fig. 2: *In vitro* drug release profile for diclofenac sodium of formulations F4, F5, F6& F7 Release Kinetics study

MATERIALS AND METHODS

The research study was conducted in HighTech Laboratory, University of Sargodha, Pakistan during January, 2014 to April, 2015. The major instruments involved in this research were include Hardness tester (Pharmatest, Germany), FTIR Apparatus (IR Pristage 21 Shimadzu, Japan), DSC Apparatus (Ta 2000 USA), Dissolution apparatus (DT 700 erweka Germany), pH meter (Ionolabwtw series 720), membrane filters (Minipore USA) and Sonicator mixer (Elma Germany). Whereas, the chemical and reagents Diclofenac Sodium, HPMC K15M, Cetyl Alcohol, Carnauba wax, Xanthan gum, Sodium Bicarbonate NaHCO3, Magnesium stearate and Talc were collected from Prim Laboratories Pvt. Ltd, Lahore, Pakistan and bought from local pharmaceutical marketed of Lahore, Pakistan.

Study design

We developed the 10 formulations of gastro retentive floating tablet of diclofenac sodium by using different combinations of polymers and gave the codes to these formulations from F1 to F10. After the development of formulations we did evaluation and characterization of formulations from F1 to F10. Evaluation and characterization was divided into 3 categories, 1st pre compression evaluation, 2nd post compression evaluation and 3rd compatibility study. In Pre-Compression evaluation we evaluated different characteristics of the powder blend/granules which includes, bulk density, tapped density, compressibility index, angle of repose and hausner's ratio. After pre-compression evaluation granules were compressed to make tablets and after that we did post-compression evaluation which includes, form

of tablets, tablet dimensions, weight variation, hardness, friability, *in-vitro* buoyancy, *in-vitro* dissolution and release kinetics. Compatibility between drugs and polymers was also studied by using DSC (Differential Scanning Calorimetry) and FTIR (Fourier Transform Infrared Spectroscopy).

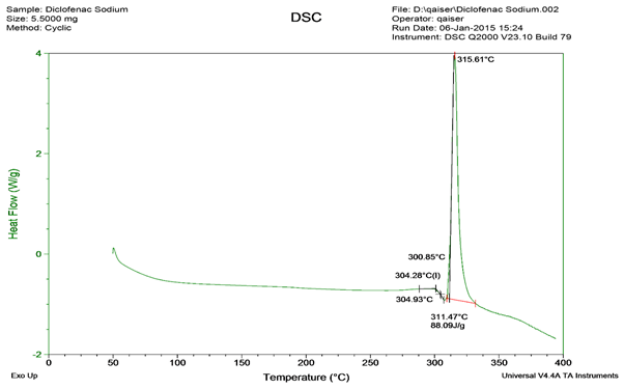

Fig. 3: DSC thermograph of diclofenac sodium

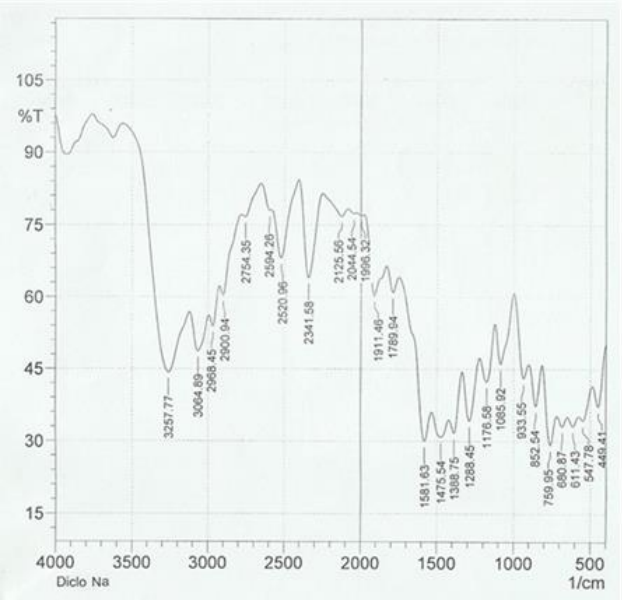

Fig. 4: FTIR spectra of diclofenac sodium

Preparation of the standard curve of diclofenac sodium

Solutions of different concentrations were prepared from 10 microgram per ml to 115 micrograms per ml by using ethanol and 0.1N HCl, absorbance was measured for each solution at lambda max of 276nm. (Subramaniyan *et al.*, 2013).

Preparation of the floating tablets by using melt granulation method

Each floating tablet consisting of 100mg diclofenac sodium was formulated by a conventionally used method of melt granulation. The compositions of tablet formulations are listed in the table with their codes. The combination of polymers was carefully chosen on the base of trial preparation. According to each formulation the required quantities of Cetyl alcohol and carnuba wax were melted in a china dish of large size on the water bath. The previously weighed and properly mixed powder blend of drugs, HPMC K15M, Sodium Bicarbonate, Xanthan Gum was added to the molten Cetyl alcohol and Carnuba wax to form a semisolid mass. After proper mixing china dish was cooled after removing from water bath. The solidified mass was then removed and then it is passed through the sieve no. 30. At the end magnesium stearate and talc were added and thoroughly mixed and then compressed to make tablets.

Pre-compression Evaluation and characterization

Pre-compression assessment of diclofenac sodium granules was carried out by using following methods:

Angle of repose

The flow properties of granules (before compression) will be characterized in terms of angle of repose, Carr's index and Hausner's ratio. The angle of repose of granules was measured by the simple funnel method. The weighed quantity of granules placed in the funnel. (Gambhire *et al.*,2007; Funnel's height was so adjusted that funnel's tip was just touching the peak of the cone of the granules. The granules were freely allowed to flow through the funnel. The diameter of the cone was measured and then calculated the angle of repose from the equation given below. (Yadav *et al.*,2010)

$\text{Tan}\,\theta = h / r$

Where, h is the height of the powder/granules cone and r is the radius.

Bulk and tapped density

Both bulk (BD) and tapped densities (TD) have been measured. The 2 grams quantity of powder mixture of each formulation, shaken to break any clumps formed, was taken in a measuring cylinder of10 ml capacity. After measuring initial volume of the granules/powder the cylinder was allowed to fall from the height of 2.5 cm. (Saravanan *et al.*,2011)The tapping continued until there is no further changes observed in volume. BD and TD were calculated by using the following equations

BD = weight of powder blend / untapped volume of packing

TD = weight of powder blend / tapped volume of packing

Carr's index

It is a test to assess the ability of the powder to be compressed or the rate at which it packed down, It is measured by measuring the BD and TD of powder and putting the values in following formula.

Carr's Index = [TD – BD] / TD x 100

It is frequently used in the pharmaceuticals as an indicator for the powder's flow ability. Value of Carr's Index more than 25 indicates that the powder has weak flow property,

Table 1: Composition of all of the ten formulations for diclofenac sodium floating tablets

No.	Ingredient	Formulation (Quantities in mg)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Diclofenac Sodium	100	100	100	100	100	100	100	100	100	100
2.	HPMC K15M	66	66	66	66	66	66	66	66	66	66
3.	Carnuba Wax	20	20	30	40	50	60	70	80	90	95
4.	Cetyl Alcohol	65	65	55	45	35	30	20	10	0	0
5.	Sodium Bicarbonate	0	0	10	20	30	30	30	40	50	60
6.	Xanthan Gum	90	90	80	70	60	55	55	45	35	20
7.	Magnesium Stearate	6	6	6	6	6	6	6	6	6	6
8.	Talc	3	3	3	3	3	3	3	3	3	3
9.	Total Weight	350	350	350	350	350	350	350	350	350	350

Table 2: Angle of Repose and Carr's Index

Flow	Angle of repose (θ)	Carr's index (%)
Excellent	<25	5-15
Good	25-30	12-16
Fair to passable	30-40	18-21
Poor	> 40	23-35
Very Poor		33-38
Extremely Poor		>40

and value less than 15, indicates good flow ability of the powder.

Hausner ratio

Carr index is related to Hausner ratio, further evidence of the ability of the flow, by the formula,

Hausner ratio = Bulk Volume / Tapped Volume

RESULT

The evaluated for physical characterization of the designed formation shown the hardness (4.6-5.1), friability (0.20-0.43%), weight variation (350 ±2 - 350±5) and *in vitro* buoyancy were found within official limits of United Stated Pharmacopoeia (USP). Whereas, the F-7 showed most optimized intra gastric floating characteristics and exhibited 93.87% release of diclofenac sodium in 9 hours. The Floating Lag Time of 8 minutes and Total Floating Time (TFT) ≥12 hours were recorded. The time period up to which the tablet remained buoyant is described as Total Floating Time (TFT). Whereas, the time required for tablet to rise to the surface and float is defined as Floating Lag Time (FLT). So, the prepared tablets were studied for *In vitro* buoyancy study in 0.1M HCl at 37°C +0.5. Formulations with low quantity of sodium bicarbonate took more time to float and the formulations with large amount of sodium bicarbonate had very short floating lag time but showed less total floating time and vice versa. According to the results formulations with low floating lag time and having total floating time more than 12 hours were selected for the *in-vitro* dissolution study. Selected formulations were F4, F5, F6, F7. Whereas, the results of FLT and TFT, four formulations were selected for the testing of *in-vitro* dissolution and drug release and rest of the 6 formulation were rejected due to more FLT or less TFT. Selected formulations were F4, F5, F6 and F7.

In-vitro dissolution study was conducted for the selected formulationsF4, F5, F6 and F7of diclofenac sodium in 0.1N HCl solution. Study was conducted for 9 hours and cumulative drug release at different time intervals was calculated. The results are shown in the table 3 & 4. The plot of the cumulative percentage of drug release v/s time (hours) shown in figs. 2, 3 & 4.

Table 3: Standard calibration curve of diclofenac sodium

Sr. No.	Concentration ug/ml	Absorbance
1.	10	0.108
2.	20	0.32
3.	30	0.532
4.	40	0.744
5.	50	0.956
6.	70	1.38
7.	90	1.804
8.	115	2.334

Drug release mechanism was determined by putting the values of release data into kinetic equations. Formulations were found to follow Zero Order, First Order and peppas model. According of drug release profile of Diclofenac Sodium Formulations F4 followed First Order and Peppas

Table 4: *In-vitro* drug release profile (diclofenac sodium) of formulation F4, F5, F6 & F7

Time (hrs.)	F4	F5	F6	F7
0	0.00	0.00	0.00	0.00
1	26.40	14.87	18.27	15.15
2	31.35	18.58	25.43	24.04
3	54.97	23.64	36.80	36.72
4	50.18	33.10	45.81	46.65
5	65.43	44.56	51.73	55.99
6	75.65	59.47	60.81	65.50
7	78.98	70.65	68.15	73.82
8	84.19	75.39	74.93	84.97
9	84.66	81.23	83.07	93.87

Table 5: Model fitting of the release profile of diclofenac sodium using four different models

Formulation	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas	Value 'n'
F4	0.8438	0.9876	0.9800	0.9861	0.574
F5	0.9834	0.9299	0.8485	0.9861	0.574
F6	0.9601	0.9867	0.9517	0.9983	0.740
F7	0.9911	0.9577	0.9113	0.9993	0.867

model, F5 followed Zero Order and Peppas model, F6 followed Peppas mode and F7 release the drug with zero order kinetics and also followed Peppas model. The value of 'n' was in the range 0.574- 0.867 which depicts drug release by anomalous transport and polymer erosion. Thus, our finding are in line with Gambhire *et al*., (2) who develop an *in vitro* evaluation of an oral floating matrix tablet formulation.

Moreover, the DSC has been used to detect any incompatibility in the formulations due to drug polymer interaction and thermo grams of pure drugs, pure polymers and of formulations are shown in figs. 3. In the scheme of DSC heat of pure diclofenac Sodium showed endothermic peak at 307C^{o}.

DISCUSSION

The effects of various components and its focus on the release of drugs is studied. Our finding are substantiated by Alzaher *et al*., (1) who reported the formulations with equal amount of drugs, main polymer, lubricants and glidant.

The value of 'n' in aforesaid study was in the range 0.574-0.867 which depicts drug release by anomalous transport and polymer erosion. Thus, our finding are in line with Gambhire *et al*., (2) who develop an *in vitro* evaluation of an oral floating matrix tablet formulation.

Additionally, to make sure of the quality and quantity analysis by FTIR a mixture of pure and blended polymers used in the composition. (Munjal *et al*., 2015) The IR spectra of pure drugs and pure polymers compared with the infrared spectra of the different formulas Polymer mixtures of drugs. Infrared spectra of diclofenac sodium exhibited characteristic peaks at 1581.63cm^{-1} due to the-C =O stretching from the carboxyl ion & at 759.95cm -1 due to C-Cl expansion. Carnauba wax offered distinct peaks in 2860.43 to 2920.23cm^{-1} due to CH_2 stretching vibrations, in 2847.8 cm^{-1} because C-CH_3 stretching vibrations while the signal resulting from the carboxyl group appeared in 1722.43cm^{-1}. Cetyl alcohol shows C=O stretching vibration at 1639.49, the peak in 1018.41cm due to C-OH Stretching vibration. Xanthan gum have the peaks of C-CH_2, C-OH, C=O at the range of 2893.22, 1037.7, 1612.49 to 1722.43 respectively. Thus, there was no any chemical reaction with the diclofenac sodium and polymers reported. (Taha *et al*., 2015)

CONCLUSION

In conclusion, the gastro-retentive effervescent floating diclofenac sodium tablet may be developed to use in actual clinical practice. The floating tablets were prepared by incorporating different combinations of polymers. Moreover, the findings of pre-compression and post-compression were also satisfactory and within the official limits. In addition of that, the F-7 showed the most promising results. That can potentially be developed to get more desirable properties and drug release profile.

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