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Formulation and Release Kinetic Study of Sustained Release Pellets of Diclofenac Sodium

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ABSTRACT

In the present work, we have explored the use of the classic polymer in combination for the floating sustained release of Diclofenac sodium. The effect of different polymer ratio has been evaluated by using the *in vitro* dissolution and buoyancy testing. It was found that the density of polymers affects the floating behavior. The Micromeritics properties of prepared batches were studied, which seems to fall within the specified limits. Polymer compatibility has been studied by using FT-IR analysis. The release kinetics of prepared five different batches has been studied, F1 was selected as an optimized batch, the total drug release in 10Hr is found to be 99.9%.

INTRODUCTION

Oral controlled drug delivery systems represent the greatest popular form of controlled drug delivery systems (CDDS) for the obvious benefits of oral route of drug administration (1, 2). CDDS is an ongoing advancing system as one of the site-specific drug delivery systems. This delivery system, by means of a combination of one or more controlled release mechanisms, can enable the drug release in the upper part of the gastrointestinal (GI) tract and colon following oral administration.(3)A necessary characteristic of controlled release delivery system is that the period of drug action should dictate the characteristics of drug molecules. There are different mechanistic approaches for the design of oral controlled release drug delivery systems such as matrix, reservoir, osmotic pressure, ion exchange resins, reformed density etc. The main challenge in developing an oral controlled-release drug delivery system is sustaining the drug release and maintaining the dosage form in the gastrointestinal tract (GIT) for an extended period of time (4). The major limitation of most currently available oral drug delivery systems is a fast gastric-emptying time. Therefore, the past few decades have seen an increased interest in gastric drug retention (5). The floating sustained-release effervescent capsular system was developed to allow the tablets to be released in the upper part of the GIT and overcome the inadequacy of conventional tablets. The Sustained-release (SR) oral drug delivery system is proven to be effective in achieving optimal drug plasma concentration through the consumption of a single dose while maintaining the therapeutic value in the blood throughout its desired period of time (6, 7).

Also, some attempts were made earlier by the researchers for taste-masked effervescent microcapsules(8) are provided each microcapsule containing an effervescent admixture microencapsulated with Ethylcellulose, they being used in formulating taste masked effervescent chewable tablets also containing microencapsulated, unpleasant tasting drugs such as non-steroidal, anti-inflammatory, NSAID drugs.(9)Gastro-retentive systems can significantly prolong the gastric residence time of drugs. The drug bioavailability of pharmaceutical dosage forms influenced by a various factor. If a drug is stable in gastric acid, prolonged gastric retention improves bioavailability reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. One of which is gastric residence time (GRT). (10, 11)The gastric emptying process from the stomach to small intestine generally lasts from a few minutes to twelve hours. This variability leads to an unpredictable bioavailability of an orally administered dosage form. Furthermore, the

relatively short gastric emptying time can result in an incomplete release of drug from the dosage form. Floating drug delivery system (FDDS) is one of the gastro-retentive dosage forms that could prolong GRT to obtain sufficient drug bioavailability. (12-15) In present work Diclofenac sodium (DCL) an acid insoluble NSAIDs used as a model drug. This drug requires multiple dosing due to its short biological half-life and it may lead to fluctuation in the plasma drug concentration and may fail to release the drug at the desired amount, which often results in poor patient compliance and inefficient therapy.(16, 17) Sustained release pharmaceutical capsules suitable for oral administration and particularly suitable for sustained release therapy with certain drugs that have absorption at upper GIT. Thus, in this study, an attempt has been made to prepare sustained release floating pellets enclosed in capsules. The prepared pellets were evaluated for drug content, infrared spectroscopy, *in vitro* floating properties and *in vitro* release drug behavior, which further filled in transparent hard shell capsules.

MATERIALS AND METHODS

1. Materials:

All chemicals were obtained from a commercial supplier and used as received. Diclofenac sodium received as gift sample from Marksans Pharma Limited, Goa. Sodium alginate and Gum acacia were purchased from Genuine chemicals co. Mumbai.

2. Methods:

2.1 Standard calibration curve of Diclofenac sodium (DCL): Solutions ranging from 2 to 10 µg/mL (ppm) were prepared by using ethanol and 0.1 N HCl Absorbance was measured for each solution at λmax of 276 nm, using Systronic 2207 UV Spectrophotometer. The correlation coefficient was found to be 0.9998 in 0.1 N HCl.

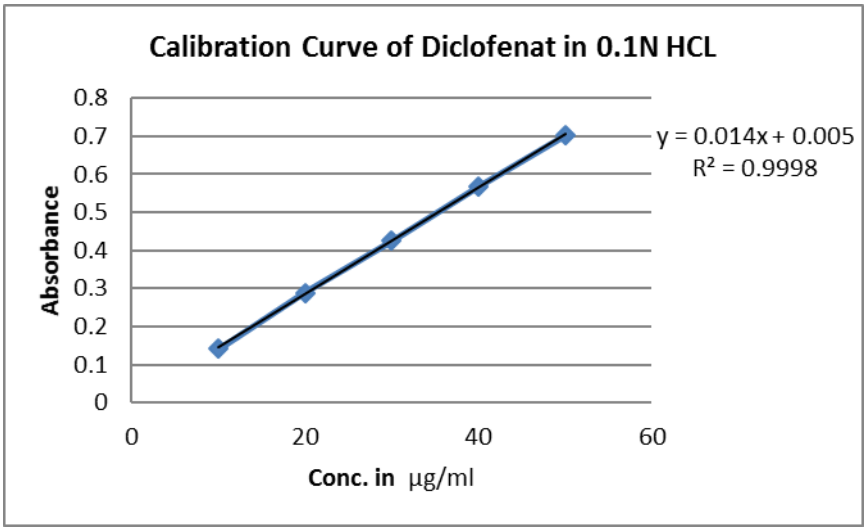

Figure 1: Calibration Curve of Diclofenac in 0.1N HCL

2.2 Preparation of SR Floating pellets containing Diclofenac sodium:

All materials were weighed, mixed and properly homogenized by mortar and passed through sieves. HPMC K4M Dissolved insufficient amount of ethanol-water mixture to act as a binder solution. Remainder materials mixed and prepared a dump mass using binder solution. The resultant wet powder mass was extruded using a radial screw extruder (Niro E140, U.K.) fitted with a screen of 1 mm thickness with 1 mm diameter circular dies. The obtained pellets were subjected to spheronizer; Spheronization was carried out at 600 rpm. Dried at room temperature. Talc in given percentage was then mixed-up and preceded for Micromeritics studies.

Table 1: Formulation Composition of DCL SR Pellets

Batches	Drug (mg) DCL	Quantities in %				
		Na-Alginate	Gum Acacia	Carbomer-934P	HPMC K4M	Talc
F1	50	70	50	10	10	0.01
F2	50	50	30	10	15	0.01
F3	50	30	-	10	20	0.01
F4	50	10	10	10	15	0.01
F5	50	70	-	10	25	0.01

2.3. Micromeritics Analysis of Floating SR Pellets:(18)

A. Flowability testing: The Flowability of the prepared powders was tested by measuring their angle of repose. The calculations of Carr's compressibility index as well as Hausner's ratio were also tested.

B. Measuring the angle of repose: The fixed height cone method was adopted where the diameter of the formed pile:

$$\Theta = \tan^{-1} (h / r)$$

Θ = Angle of repose, h = Height of the pile and r = Average radius of the powder pile.

2.4.Determination of the initial and tapped bulk densities:

A fixed weight of the powder either the drug or the prepared pellets was poured into a 10 mL graduated cylinder, the powder was allowed to settle with no outer force and the volume occupied was measured as VI (initial bulk volume). The cylindrical graduate distance until a constant volume was obtained.

2.5.Determination of drug retained and yield of floating SR Pellets: Measured quantity of Pellets equivalent to 50mg of DCL was dissolved in 50 mL of 0.1N HCl, kept for 10 hr. for the stirring on the magnetic stirrer at 50 rpm. After that, the swelled pellets separated from the solvent, filtered and samples were assayed for drug content by UV-spectrophotometry (Systronic 2207) at 276 nm No interference was found due to the other floating pellets components at 276 nm. The percentage drug retained and yield was calculated as follows: (19)

$$\%\ Drug\ Retained = \frac{Calculated\ Drug\ Conc.}{Theoretical\ Drug\ Concentration} \times 100$$

$$\%\ Yield = \frac{Total\ Wt.of\ Floating\ Granules}{Total\ Wt.of\ Drug\ and\ Polymers} \times 100$$

2.6.Determination of Floating Behavior of Pellets:

The obtained pellets were studied for buoyancy and floating time using USP Apparatus II (paddle type). One hundred grams of pellets each batch were placed in 900 ml of 0.1 N HCl

(pH 1.2) containing 0.02% w/v Tween 80 and agitated at 50 rpm, the temperature was maintained at 37ºC. (20)

2.7.Fourier transform-infrared (FTIR) analysis: Preliminary confirmation of Drug and prepared SR Pellets were done by using FTIR spectrophotometer (IR Affinity-1, Shimadzu Japan). 1:100 ratio of the sample mixed with dried KBr powder, examined under spectrometer. Using diffuse reflectance spectrum the transmission was calculated after scanning sample from 4000 – 400 cm^{-1}

2.8.*In-vitro* Release Kinetics Study of Floating SR Pellets:

From each formulation, pellets subjected to the dissolution test. *In-vitro* dissolution studies were performed using USP apparatus II (paddle type), at a speed of 50 rpm in 1.2 pH buffer solution. The whole system of the dissolution test was thermally controlled at 37°C. At 30 minutes time intervals aliquots of 5.0 mL of the samples were withdrawn at each hour for a total of 10 hr. The samples were filtered and then analyzed at UV spectrophotometer (Systronic 2207) at a wavelength of 276 nm.

RESULTS AND DISCUSSION

1) Micromeritics Analysis of Sustained Release Pellets:

Micromeritic properties of the prepared pellets calculated by previously mentioned formulae:

Table 2: Micromeritics Evaluation of SR Pellets

Sr. No.	% Drug Retained	% Yield	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle of Repose
1.	13.20	92.1	0.32	0.59	36.0	1.56	21.33
2.	12.60	89.3	0.57	0.80	28.7	1.40	22.66
3.	11.70	85.4	0.63	0.86	27.1	1.06	21.66
4.	12.00	83.3	0.93	0.88	22.5	1.17	23.33
5.	11.40	82.5	0.90	0.90	26.2	1.64	21.00

Table 3: Micromeritics Evaluation of Optimized Batch (F1)

Sr. No.	Parameters	Results
1.	% Drug Retained	13.2
2.	% Yield	92.1
3.	Bulk Density	0.32
4.	Tapped Density	0.59
5.	Carr's Index	36.0
6.	Hausner's ratio	1.56
7.	Angle of repose	21.3^0

2) Determination of drug retained and yield of floating SR Pellets: Measured quantity of Pellets equivalent to 50mg of DCL was dissolved in 50 mL of 0.1N HCl, kept for 10 hr. for the stirring on the magnetic stirrer at 50 rpm. After that, the swelled pellets separated from the solvent, filtered and samples were assayed for drug content by UV-spectrophotometry (Systronic 2207) at 276 nm No interference was found due to the other floating pellets components at 276 nm.

3) FT-IR Analysis: The FT-IR spectrum shown in Figure 2. The IR spectrum of pure drug Diclofenac sodium shows a characteristic peak at 3388 cm^{-1} due to N-H stretching frequency of secondary amine. The absorption bands at 1305 and 1282 cm^{-1}resulted from C-N stretching and the peaks at 1556 and 1574 cm^{-1}due to C=C stretching and C=O stretching of a carboxylate group, respectively. The C-Cl stretching characteristic peak was observed at 746 cm^{-1}. The IR spectra of Diclofenac sodium with Na-Alginate (Fig.2-B) and Diclofenac sodium with Carbomer-934P (Fig.2-C) shows all the principal characteristic peaks related to Diclofenac sodium without any change in their position, representing no possibility of chemical interaction between the drug and formulation components. Peak assignments of Gum acacia show a broad absorption band at 3384 cm^{-1}. This band is the characteristic of the glucosidic ring and is also due to stretching vibration of O-H. The peak at 2934 cm^{-1} attributed to C-H stretching of the polysaccharide. The characteristic peak at 2130 cm^{-1} arises from C=O stretching of various carbonyl species of the gum. The broad peak at 1635 cm^{-1}corresponds to asymmetric C=O stretching of carboxyl groups. The symmetric C=O stretching of a carboxylic acid of glucuronic acid appears at 1420 cm^{-1}. The peak at 1062 cm^{-1} is assigned to C-O stretching of the saccharide structure. The C-H out of plane bending vibration positioned at 601 cm^{-1}. (21, 22)

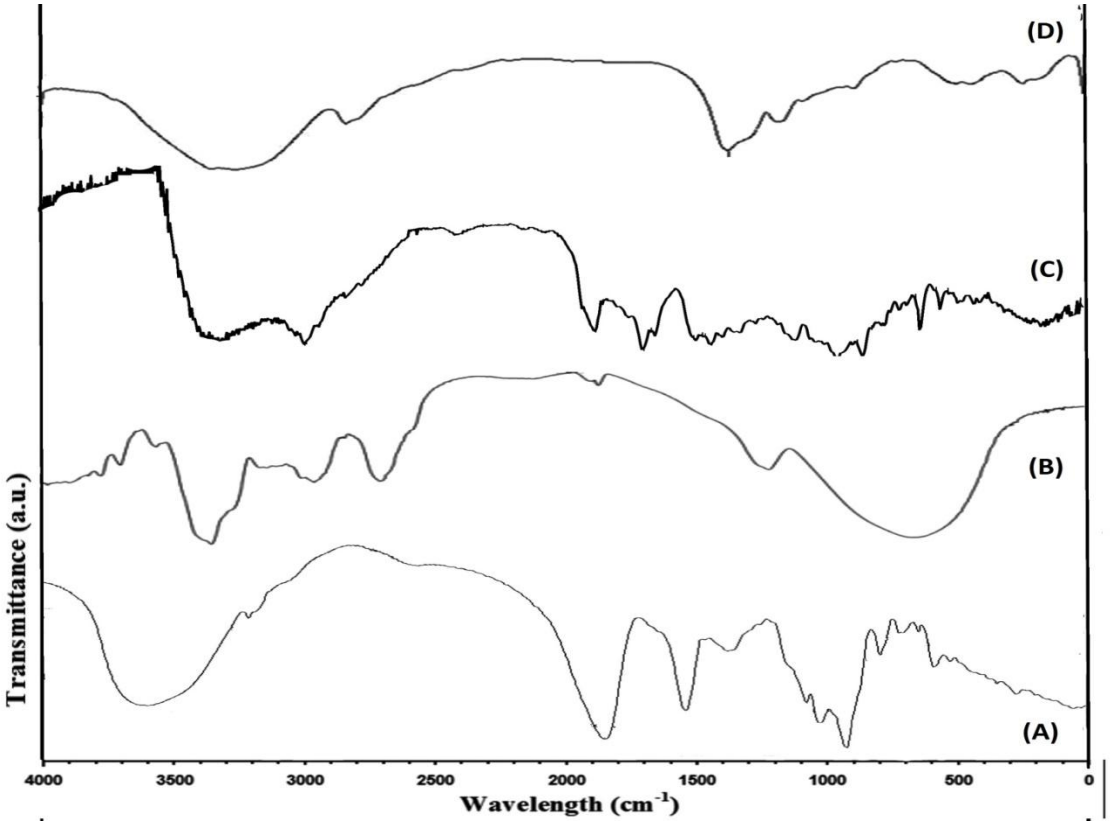

Figure 2: Showing FT-IR Spectra of (A)Pure Diclofenac Sodium, (B) Gum Acacia, (C)Carbomer-934P and (D) Sodium Alginate.

4) Floating Characteristics of Granules Pellets: Percentage buoyancy of all formulation was calculated by subjecting the weighed amount of pellets in a USP II Apparatus under the previously mentioned conditions. The floating portion of pellets and the settled portion of pellets were recovered separately. Buoyancy percentage was calculated as the ratio of the proportion of that remained floating and a total number of pellets taken (11), Total Floating Time (TFT) is the time period to which pellets remained float on the surface of the basket, Which successively measured prior to the dissolution testing and noted.

Formulation Factors that Affect the Release Kinetics: The physical properties of the polymers influences the formulation variables on the release kinetics of Diclofenac had been studied. They were the polymer excipients, the contents and density of the polymers. Preliminary study results indicated that DCL exhibited a sustained-release behavior in the presence of Carbomer-934P and Gum Acacia.

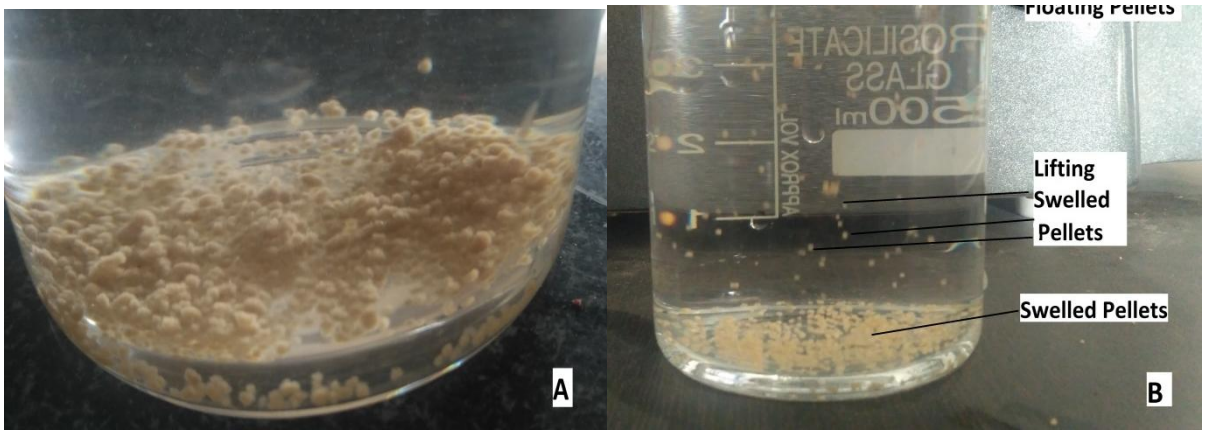

Figure 3: Images showing the swelling (A) and floating (B) properties of the DCL SR pellets

Table 4: Results showing the effect of polymers ratio and its effects on; *In-vitro* Buoyancy Study, Floating time of DCL SR Pellets

Batches	Drug: Na-Al: Gum-A Ratio	Buoyancy Lag Time (Min.)	Total Floating time (Hr.)	Drug Content (mg)
F1	1:1.4:1.0	1.05	10.2	48.7
F2	1:1.0:0.0	1.28	9.4	48.2
F3	1:0.6:0.0	1.47	9.1	48.09
F4	1:0.2:1.4	1.39	9.0	47.7
F5	1:1.4:0.0	1.34	9.2	47.9

1) *In vitro* Drug Release Kinetics Study of Floating SR Pellets: The release of Diclofenac sodium in 0.1 N HCl was generally low compared to that in buffer pH 6.8 for all formulation ratios studied. This is due to the fact that the drug is a weak acid (p*K*a 4.15) and therefore it will be unionized and of lower solubility at lower pH values. (23)

Table 5: Correlation Coefficient (R^2) and Drug Release of DCL SR Pellets

Batches	Correlation Coefficient (R^2)	% Drug Release after 10 Hours
F1	0.9556	99.9
F2	0.9683	97.5
F3	0.9317	95.7
F4	0.9406	96.3
F5	0.9245	96.7

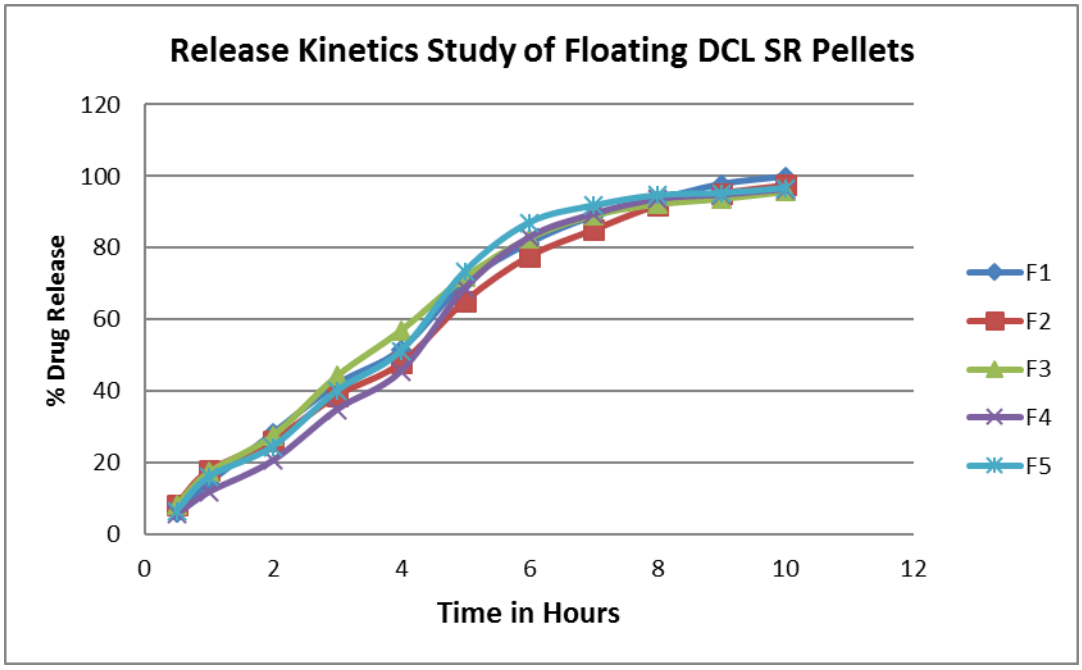

Figure 4: Release Kinetics Study of Floating DCL SR Pellets

CONCLUSION

A novel concept of utilization density based buoyancy properties for gastroretentive floating type SR drug delivery system have been explored. The prepared pellets were evaluated for micromeritic and release behaviors to study the effect of the polymers and its concentrations as the pellets showed excellent floating and sustaining properties. The prepared pellets have scalable aspects, can be filled in a hard shell capsule or can be subjected to the tablet compression.

CONFLICT OF INTEREST

Authors declares no conflict of interest

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