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Formulation and Evaluation of Modified Disintegrating Sustained Release Tablets of Diclofenac Sodium

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Abstract

Oral drug delivery is the largest and the oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration. In oral drug delivery, the sustained release (SR) tablets maintains the desired drug concentration for prolong period of time, reduced 'see- saw' fluctuation, reduced total dose, improved efficiency in treatment. But many patients like paediatric, geriatric and also patients may have difficulty in swallowing (Dysphagia) find it difficult to swallow tablets and thus do not comply with prescription. This problem is overcome by formulating and developing modified disintegrating sustained release tablets. In this case, first microspheres of the drug are formulated by using any suitable technique. And then optimized microspheres formulation is further formulated in to the fast disintegrating tablets (FDT) by using superdisintegrants. So that after taking such a tablets, the tablet only disintegrates into the mouth then microspheres are separated and ingestion of such microspheres starts releasing drug for prolonged period of time. This concept fulfills both the advantages of sustained release and fast disintegrating tablets.

KEYWORDS: Oral drug delivery, Sustained release (SR) tablets, Fast disintegrating tablets (FDT), Microspheres, Superdisintegrants.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of

pharmacokinetic and pharmacodynamic profiles with acceptable level of safety to the patient [1].

In recent years a wide variety of newer oral drug delivery systems like sustained/controlled release dosage forms are designed and evaluated in order to overcome the limitations of conventional therapy. These products are able to maintain steady drug plasma levels for extended

periods of time, reduced total dose, improved efficiency in treatment as a result the variations of the drug levels in the blood are prevented and minimized drug related side effects [2,3]. But many patients like paediatric, geriatric and also patients may have difficulty in swallowing (Dysphagia) find it difficult to swallow tablets and thus do not comply with prescription. This problem is overcome by formulating and developing modified disintegrating sustained release tablets.

Microspheres is well accepted formulation employed to sustain the drug release and reduce or/ eliminate gastrointestinal irritation, dose intake and ultimately improve the compliance in the pharmacotherapy of arthritis, inflammation and pain [4,5]. United States Food and Drug Administration (FDA) defined FDT as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue.'' FDT has several advantages like beneficial for travelling patients, easy to administered for geriatric, paediatric patients, excellent mouth feel property, beneficial for patients may have difficulty in swallowing (Dysphagia), no need of water [6]. In this case, first microspheres of the drug are formulated by using any suitable technique. And then optimized microspheres formulation is further formulated in to the fast disintegrating tablets (FDT) by using superdisintegrants. So that after taking such a tablets, the tablet only disintegrates into the mouth then microspheres are separated and ingestion of such microspheres starts releasing drug for prolonged period of time. This concept fulfills both the advantages of sustained release and fast disintegrating tablets.

Diclofenac Sodium is a potent non-steroidal anti-inflammatory drug, which is a commonly prescribed drug for the treatment of patients suffering with pain, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is a weak acid (pka = 4) practically insoluble in water and acidic environment but highly permeable (class 2) according to the biopharmaceutical classification system (BCS). The oral absorption is uniform, rapid and complete with a bioavailability of nearly 64% and an diclofenac sodium is reported to have a

short biological half-life (2 ± 0.5 h) requiring it to be administered in 100mg twice daily. To reduce the frequency of administrations and improve patient compliances, Diclofenac sodium is suitable candidate for making sustain release dosage form [7].

MATERIALS AND METHODS

Materials:

Diclofenac sodium was obtained as a gift sample from Gift sample from Arati Drugs Ltd, Mumbai, India. Microcrystalline cellulose (Avicel), magnesium stearate, sodium alginate and calcium chloride were purchased from Loba Chemie Mumbai, India. Crospovidone, sodium starch glycolate and mannitol were purchased from Molychem, Mumbai. All chemicals used were of analytical reagent grade and double distilled water was used throughout the experiments.

Methods:

Preparation of Microspheres

Microspheres are prepared by Ionotropic gelation technique. Here, required amount of carbopol was dispersed in a specified volume of cold water containing the drug and allowed to swell for 2 hours. In another beaker suitable amount of sodium alginate was taken and mixed well with specified volume of water. The carbopol solution containing the drug was added to sodium alginate solution with stirring to produce a viscous form. Then polymer drug solution was added drop wise by using syringe of 21 G in diameter from a height of about 5 cm into a beaker containing 4% w/v solution of calcium chloride with continuous stirring by magnetic stirrer (Figure1). Then the solution containing the gel formed microspheres was filtered by using Whatman filter paper No-1. The microspheres were allowed to dry at about 30 to 40°C for 2-3 days and stored in well-closed container for further use (Table 1) [8, 9].

Evaluation of Microspheres

Particle Size Analysis

Particle size of all batches of microspheres were determined by using Digital microscope.

Drug entrapment efficiency and drug loading

The amount of Diclofenac sodium present in the microspheres was determined by taking the known amount of microspheres in which 100 mg of drug should be present theoretically. Then the microspheres ware crushed and the powdered microspheres was taken and dissolved in 100 ml of phosphate buffer (pH7.4) solution and stirred for 15 min with an interval of 5 min and allowed to keep for 24 hrs. Then the solution was filtered through Whatman No.1

filter paper. Then the absorbance was measured spectrophotometrically at 274 nm concentrations were determined by employing simultaneous equation: Y= mx+c

Drug Entrapment Efficiency (%) = [Experimental drug Content/ Initial Drug Content into the Formulation] ×100

Drug Loading (%) = [Qm / Wm] × 100,

Where, Wm = weight of the microspheres; Qm = quantity of the drug present in the microspheres.

Swelling study (Degree of swelling)

Microspheres (50 mg) were placed in little excess of distilled water, 0.1N HCl and PBS (pH 7.4) and allowed to swell to constant weight. The microspheres were removed, blotted with filter paper and their changes in weight were measured at an interval period of 10 min and recorded. The degree of swelling (a) was then calculated from the formula:

$a = W_G - W_O / W_O$

Where, Wo is the initial weight of the microspheres and W_G is the weight of the microspheres at equilibrium swelling in the medium.

***In vitro* release study**

The dissolution process was carried out in USP dissolution rate test apparatus [Apparatus-II (paddle method), 75 rpm, 37±0.5^0 C] taking microspheres equivalent to 100 mg diclofenac sodium in 900 ml of 2% SLS in 0.1 N HCl media for first 2 hrs, followed by 900 ml 1% SLS in pH 6.8 phosphate buffer for next 10 hrs. The media of pH 1.2 (0.1N HCl) was chosen to represent the gastric condition; pH 6.8 was a compromise condition between the pH of the gastric and small intestine**.** Aliquots samples were withdrawn for cumulative drug release at specified time intervals and replaced with same volume of fresh media, filtered and analyzed spectrophotometrically at 275nm for pH 1.2 and 274nm for pH 6.8 buffer [10-12].

Formulation of tablets

Fast disintegrating tablets were prepared using super disintegrants addition. Different ratio of microcrystalline cellulose and superdisintegrant were used. The ratio giving the best disintegration time along with optimum hardness was chosen and tablets prepared by direct compression. Accurately weighed microspheres were properly mixed with Microcrystalline Cellulose, Superdisintegrant and Mannitol for about 10-15 min. Then magnesium stearate was added and mixed for further 2 min and compressed into tablets (Table 2).

Evaluation of the tablets

The prepared tablets were evaluated for thickness, weight variation, hardness, friability, drug content, wetting time, disintegration time and *In- vitro* dissolution time as per the official methods.

Thickness

The thickness of the tablets was determined using a Vernier caliper.

Weight variation

Randomly, twenty tablets were selected after compression and the mean weight was determined using an electronic balance. None of the tablets deviated from the average weight by more than ±5%.

Hardness

The crushing strength of the tablets was measured using a Pfizer hardness tester.

Friability

Ten tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted and reweighed. The percentage friability of the tablets was measured as per the following formula,

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug content

The tablet from each formulation was crushed and powdered material was taken. Then dissolved in 100 ml phosphate buffer (pH 7.4) solution and stirred for 15 min with an interval of 5 min and allowed to keep for 24 hrs with occasional stirring. Then the solution was filtered through Whatman No.1 filter paper. Then the absorbance was measured spectrophotometrically at 274 nm against phosphate buffer (pH 7.4) solution as blank with the help of UV spectrophotometer and concentrations were determined by employing simultaneous equation: Y= mx+c. Three tablets from each formulation batch were tested randomly and the average reading noted.

Wetting time

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 9ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted.

***In vitro* disintegration time**

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The phosphate buffer pH 6.8 was used as a medium and temperature of 37°±2°C was maintained. The time taken for the entire tablet to disintegrate completely was noted.

***In vitro* release study**

The dissolution process was carried out in USP dissolution rate test apparatus [Apparatus-II (paddle method), 75 rpm, 37±0.5^{0}C] taking prepared tablet of diclofenac sodium in 900 ml of 2% SLS in 0.1 N HCl media for first 2 hrs, followed by 900 ml 1% SLS in pH 6.8 phosphate buffer for next 10 hrs. The media of pH 1.2 (0.1N HCl) was chosen to represent the gastric condition; pH 6.8 was a compromise condition between the pH of the gastric and small intestine**.** Aliquots samples were withdrawn at specified time intervals and replaced with same volume of fresh media, filtered and analyzed spectrophotometrically at 274nm for cumulative drug release [14-16].

RESULTS AND DISCUSSION

Evaluation of Microspheres

Particle Size Analysis

Particle size can be determined by using Digital microscope. The mean diameter of diclofenac sodium microspheres was found in between 79.36±0.43 to 90.20±0.34 µm (Table 3).

Drug entrapment efficiency and drug loading

The percent encapsulation efficiency was increased upto 80.4±0.26 % with increasing polymer concentration (Table 4).

Swelling study (Degree of swelling)

Prepared microspheres swell in distilled water, 0.1N HCl and phosphate buffer 6.8 (Table 5).

***In vitro* drug release study**

The dissolution process was carried out in USP dissolution rate test apparatus [Apparatus-II (paddle method), 75 rpm, 37±0.5^0 C] taking microspheres equivalent to 100 mg diclofenac sodium in 900 ml of 2% SLS in 0.1 N HCl media for first 2 hours, followed by 900 ml 1% SLS in pH 6.8 phosphate buffer for next 10 hours. (Figure 2).

Formulation of tablets

Among all the formulations of microspheres F1 to F7, F7 shows good mean particle size, drug entrapment efficiency, drug loading, degree of swelling and good *In- Vitro* drug release data. So, F7 formulation was chosen for the preparation of the fast disintegrating tablets.

Evaluation of the tablets

In the present study fast disintegrating tablets of diclofenac sodium microspheres were prepared by using Crospovidone and Sodium starch glycolate as a superdisintegrants. Total numbers of six formulations were prepared by direct compression technique. The data obtained of post-compression parameters such as thickness, weight variation, hardness, friability, amount of drug content, wetting time and in-vitro disintegration time are shown in (Table 6 & 7).

***In vitro* release study**

In vitro dissolution studies of various formulations at the end of 12 hours are reported. (Figure 3).

CONCLUSION

The present study demonstrated the successful preparation of stable, sustained release fast disintegrating tablets of diclofenac sodium. It is a totally new concept. As such the sustained release tablets are able to maintain steady drug plasma levels for extended periods of time, reduced total dose, improved efficiency in treatment as a result the variations of the drug levels in the blood are prevented and minimized drug related side effects. But many patients like paediatric, geriatric and also patients may have difficulty in swallowing (Dysphagia) find it difficult to swallow tablets and thus do not comply with prescription. This problem is overcome by formulating and developing sustained release fast disintegrating tablets. This concept fulfills both the advantages of sustained release and fast disintegrating tablets.

Among all the formulations of microspheres, F7 formulation shows good mean particle size, drug entrapment efficiency, drug loading, degree of swelling and good *In- Vitro* drug release data. So, F7 formulation was chosen for the preparation of the fast disintegrating tablets. Among all the formulations tablets, batch S3 containing SSG (4%) was found to be the best as compare to other formulations as this formulation showed good hardness, low friability and least wetting time & disintegration time.

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Table 1: Formulations of microspheres

Code of Formulation	Drug (mg)	Polymer Carbopol (mg)	Sod. Alginate (mg)	Carbopol + Sod. alginate (mg)	Drug: Polymer Ratio
F1	100	0	100	100	1:1
F2	100	0	200	200	1:2
F3	100	0	300	300	1:3
F4	100	0	400	400	1:4
F5	100	100	100	200	1:2
F6	100	200	100	300	1:3
F7	100	300	100	400	1:4

Table 2: Formulation of FDT of diclofenac sodium

Sr. No.	Ingredients	Formulations					
		S1	**S2**	**S3**	**S4**	**S5**	**S6**
1	Microspheres	250	250	250	250	250	250
2	SSG	6	9	12	-	-	-
3	Crospovidone	-	-	-	6	9	12
4	Mannitol	15	15	15	15	15	15
5	MCC	121.5	118.5	115.5	121.5	118.5	115.5
6	Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5
	Total weight (mg)	400	400	400	400	400	400

Table 3: Mean particle size of microspheres

Sr. No.	Formulation code	Mean Particle size (µm)
1	F1	84.28±0.68
2	F2	82.12±0.22
3	F3	80.40±0.46
4	F4	79.36±0.43
5	F5	84.32±0.32
6	F6	90.20±0.34
7	F7	89.33±0.54

Table 4: Drug entrapment efficiency and Drug loading of microspheres

Sr. No.	Formulation code	DEE (%)	DL (%)
1	F1	48.44±0.66	24.22±0.33
2	F2	52.6±0.36	26.3±0.18
3	F3	56.8±0.72	28.4±0.36
4	F4	64.48±0.40	32.24±0.2
5	F5	68.90±0.48	34.45±0.24
6	F6	74.64±0.44	37.32±0.22
7	F7	80.4±0.26	40.2±0.13

Table 5: Swelling study of prepared microspheres

Sr. No.	Formulation	Degree of swelling		
		0.1 N HCL	Distilled water	Phosphate buffer 6.8
1	F1	0.27	0.42	0.82
2	F2	0.33	0.49	0.96
3	F3	0.34	0.55	1.13
4	F4	0.45	0.61	1.25
5	F5	0.54	0.70	1.30
6	F6	0.64	0.79	1.41
7	F7	0.71	0.98	1.58

Table 6: Evaluation of the tablets (S1, S2, S3)

Sr. No.	Evaluation parameters	Formulations		
		S1	S2	S3
1	Thickness (mm)	4.6	4.6	4.6
2	Weight variation (mg)	398.58	400.2	399.4
3	Hardness (kg/cm^2)	4.2±0.6	4.6±0.4	4.5±0.2
4	Friability (%)	0.72±0.4	0.74±0.36	0.56±0.4
5	Drug content (%)	99.7±0.2	100.1±0.3	100.2±0.2
6	Wetting time (sec)	44.3±1.6	42.3±2.4	39.2±2.1
7	*In- vitro* disintegration time (sec)	66.2±2.1	58.4±2.2	51.2±1.8

Table 7: Evaluation of the tablets (S4, S5, S6)

Sr. No.	Evaluation parameters	Formulations		
		S4	S5	S6
1	Thickness (mm)	4.6	4.6	4.6
2	Weight variation (mg)	399.08	401.44	400.6
3	Hardness (kg/cm^2)	4.2±0.3	4.4±0.7	4.6±0.8
4	Friability (%)	0.66±0.09	0.56±0.24	0.67±0.4
5	Drug content (%)	99.8±0.2	100.0±0.4	99.8±0.3
6	Wetting time (sec)	64.2±1.6	60.1±0.8	54.8±1.3
7	*In- vitro* disintegration time (sec)	80.4±1.6	73.1±1.5	62.1±2.0

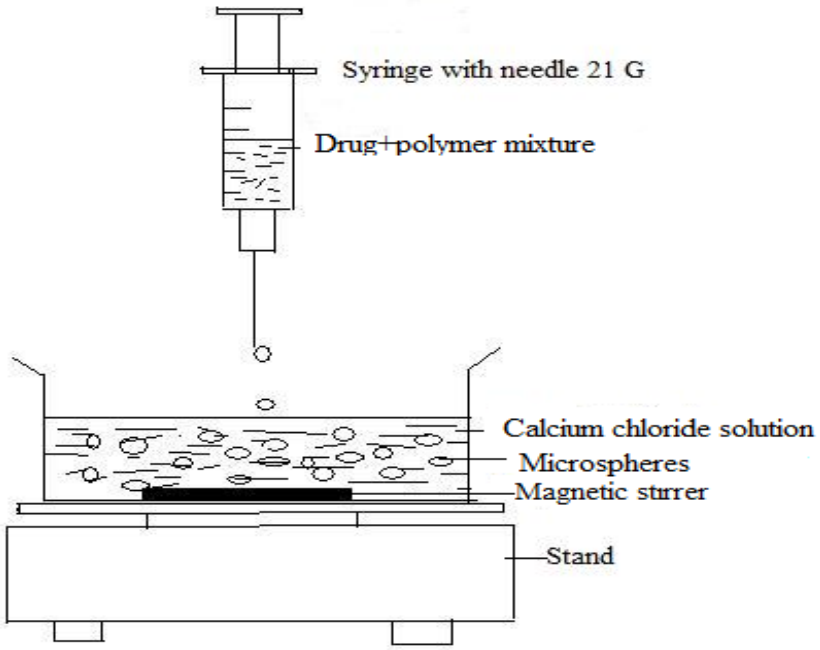

Figure1: Ionic gelation technique

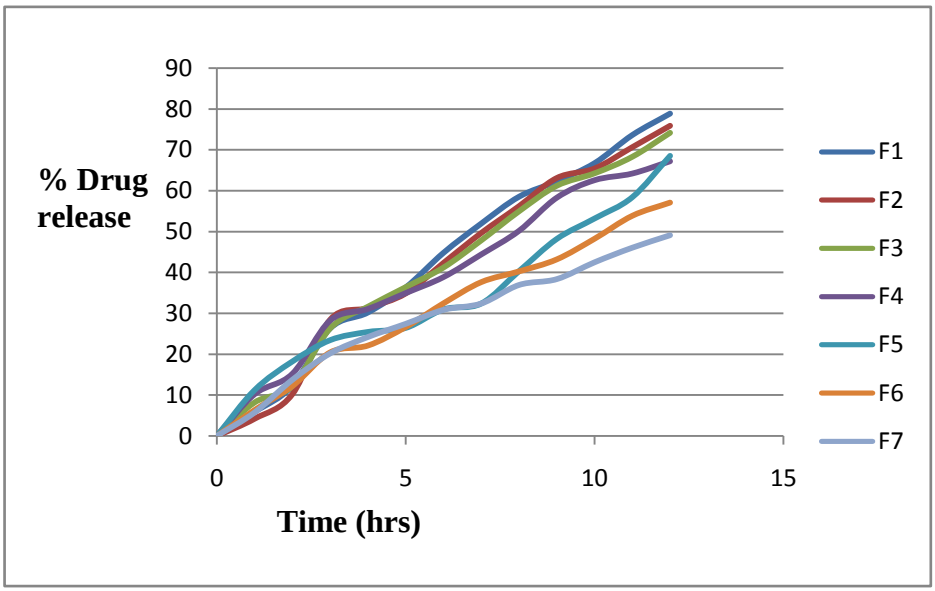

Figure 2: *In vitro* drug release study of prepared microspheres

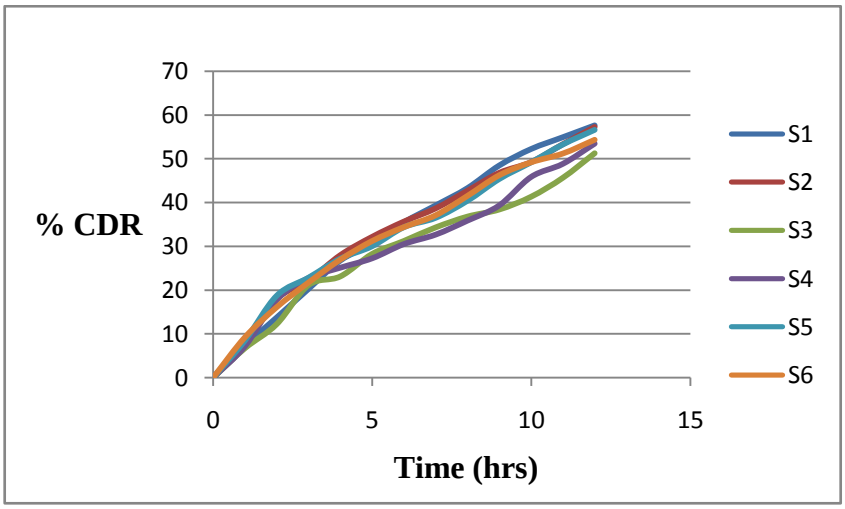

Figure 3: *In vitro* drug release study of the tablets