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Formulation and Evaluation of Radiolabeled Polymeric Microsphere of Diclofenac for Colon Targeted Drug Delivery

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Abstract

Non-steroidal anti-inflammatory medicine (NSAIDs) square measure the principally used for the treatment of inflammation, gentle and contractile organ conditions, like rheumatism and degenerative arthritis. These diseases square measure dangerous for society, wherever they're answerable for some people's disabilities (However, the clinical use of NSAIDs needs a profit-loss assessment because of side-effects like gitoxicity,nephritic toxicity and hepatotoxicity, primarily in long-run medical care. There square measure man y varieties of formulation develop for NSAIDs for the instance of muco-dhesion drug delivery system its most generally utilized in novel drug delivery system. It is a phase within which 2 surfaces, a minimum of 1 biological get command along in shut contact by surface forces for associate extended period of your time.

In this study, we will focus on a method of delivery drug delivery to the colon, which is useful for protein and amide drugs, drugs for the treatment of colitis, crown syndrome, diarrhea, and carcinoma. Colon neutral pH is a major site for high response to biological processes to reduce catalytic activity and reduce bioavailability, avoiding times of first-pass metabolism and longer transport time..Colon may be a special delivery system, which leads to uncontrolled drug use in the high channel and rapid drug entry after entering the colon. Microspheres are small in size and possess a large surface to volume ratio and the lower sized microspheres have colloidal properties.

Keywords: NSAIDs, Microspheres

Introduction

Mucoadhesive microspheres: These are mainly defined as spherical particles of 1-1000 pm consisting polymers, &other protective ingredients like natural polymers which include polylactic acid &polyglycolic acid. "Microspheres are small in size and possess a large surface to volume ratio and the lower sized microspheres have colloidal properties. The interfacial properties of microspheres are extremely important, often dictating their activity".

Classification of Microspheres-

Based on the type of microparticles:-

Micro Capsule- Mono core type and polycore type
Microsphere- Matrix-type and Reservoir Type.
Micro Capsule- Microparticle is coated with solidified polymeric envelope leading to microcapsules.
Microsphere- Microparticle is enclosed within a polymeric matrix.

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Based on the type of formulation:-
Effervescence Microsphere is prepared by swellable polymers which release C02. Polymers generally employed are methyl-cellulose, HPMC, chitosan, & other effervescent chemicals viz., NaHCO3, citric acid etc

Non effervescent microparticles:
These are formulated using a gel-forming or swellable cellulose type of hydrocolloids, polysaccharides, polyacrylate, polymethacrylate, and polystyrene. When microparticles react withgastric liquids, they attain bulk density >1&trapped within the swollenspherepermitscontrolleddelivery of drug.

Application

Medical Application:
1. Sustained delivery of proteins & hormones.
2. Hepatitis, influenza, diphtheria vaccines.
3. Insulin novel drug delivery
4. Radioactive Application:
5.Radio embolization of liver and spleen tumors.
6. Arthritis radiotherapy

Types of Microspheres-
Bio-adhesive microspheres-Adhesion of drug delivery device to the mucosal membranes can be termed as bio-adhesion.
Magnetic microspheres-Inthis, a larger amount of freely circulating drugs can be replaced by a smaller amount of magnetically targeted drugs.
Polymeric microsphere- Polymeric microspheres are divided into two t ypes- degradable and synthetic polymeric microspheres.

Benefits of colon drug delivery system-
Targeted delivery
Dose is decreased
Side effects are less
Drug utilization is more
It is a better site for poorly absorbed medicines from upper GI tract.

Drug Profile of Diclofenac
Chemical name:-2-(2,6-dichloroanalino) phenylaceticacid. In India, it is supplied as Na/K salt.

Table1: Physicochemical Properties of Diclofenac

Molecular Formula	Ct Hi iCl,NO,
Molecular Weight	296.145 g/mol
IUPAC Name	2-(2-[(2,6-dichlorophenyl)amino]phenyl} Acetic acid
Melting Point	253-255 "C
Molecular Mass	296.145 g/mol
Solubility	2.37mg/L (25"c)
Trade Name	Aclonac, Cataflam, Voltaren
Dosage Form	Solution ,Tablet, suppositories

Mode of Action-"Primary mechanism responsible for its anti-inflammatory, antipyretic, and analgesic action is thought to be inhibition of PG synthesis by inhibition of cycloox ygenase (C OX). Inhibition of COX also decreases PG in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid"

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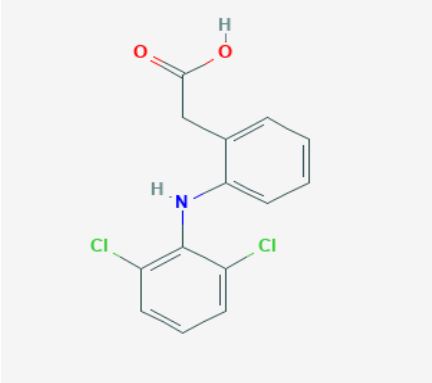

Fig. 1: Structure of diclofenac

Polymers Profile:

Natural polymers used in ionic gelation method-

Sodium alginate

Non-poisonous,
Sodium alginate is a Na salt of alginic
Sodium alginate is a Na salt of alginic
Shows cross-link with Ca and Zn
Naturally occurring polysaccharide acid

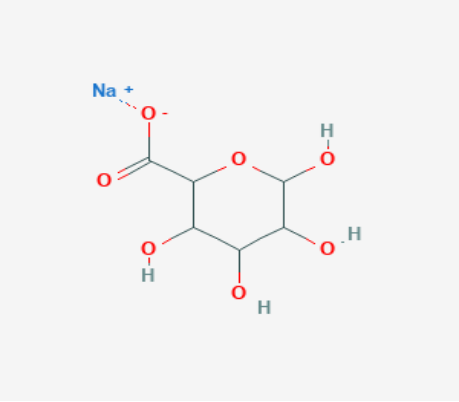

Fig. 2: Structure of Sodium alginate

Sodium Alginate is the sodium salt form of alginic acid and gum mainly extracted from the cell walls of brown algae, with chelating activity. Upon oral administration, sodium alginate binds to and blocks the intestinal absorption of various radioactive isotopes, such as radium Ra 226 (Ra-226) and strontium Sr 90 (Sr-90).
Physical Description
Nearly odourless, white to yellowish fibrous or granular powder
Color/Form
Cream-colored powder
Odor
almost odorless
Taste
almost tasteless
Solubility
Insoluble in alcohol, chloroform, ether, aq acid soln below ph 3, and in hydro-alcoholic soln greater than 30% wt/wt

Material and Methods

Formulation and evaluation of microsphere was made as per standard procedure.

Table 2: Material to be used

Name of Chemicals	Company/ Make
Diclofenac	Yarrow chem., Mumbai
Pectin	Himedia Mumbai
Ethyl cellulose	CDH, New delhi
Calcium chloride	Himedia Mumbai
Ethanol	CDH, New delhi
Sodium Bicarbonate	RFCL Limited
Sodium alginate	Lobachemie

Table 3: Types of equipments used

Instrument/Equipment	Model No	Manufacturer/ Supplier
Double beam IV Spectrophotorneter	2102	Systronics, Ahmedabad, India
Dissolution Apparatus	TDT -08L	Electro lab Mumbai, lndia
Sonicator		
Digital melting apparatus	l0l3A	Perfect, India
pH Meter	MKS	SYstronics, Ahmedabad,1ndia
Digital balance	ATX224	Shimadzu Corporation Kyoto Japan
Electronic balance	20OD	Dana Instruments Ltd., India
Water shaker	RSB- 1 2	Remi instrument Lid. India.
FTlR	BX2	Perkin Elmer N orwalk USA

Results and Discussion

Identification Studies

For the identification of API following parameters were observed and compare with standard value to observed value.

Table 4: Comparative study of melting point in test and reference.

Sr. no.	Melting Point Studies of Diclofenac (°C)				Standard Value (IP)
	Ml	M2	M3	Average Temp.	
1	285.3	288.4	284.32	286.00	286°C
2	283.4	286.3	2fi3.1	284.26	
3	287.4	287.4	284.5	286.43	

Table 5: Partition coefficient of diclofenac.

Solvent	**Partition** Coefficient of Diclofenac				Reference Value
	P1	P2	P3	Avg.	
Water	13.	13.4	13.2	13.2	13.4
pH 7.4	13.2	I 3.4	13.2	I 3.2	
PH6.8	13.1	I 3.4	12.4	I 3.1	

UV Spectrophotometer

Preparation of Standard Calibration Curve

15 mg milligrams of the drug were accurately measured and transferred into a 50 ml volumetric flask. Diluents were added in a ratio I : I for methanol and water and then sonicated for 10 minutes, further dilutions were made in different concentration. Dilution with maximum cone. was scan in U V spectrophotometer against the blank. The maximum absorbance was observed at 275 nm (Z' '275). The learning dilutions were also scanned under UV at k' *275 and the absorbance was recorded. A graph was plotted between concentration and absorbance to find out the state line equation and R'Value.

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Table 6: Absorbance table for Diclofenac

Concentration	Absorbance				
	A1	A2	A3	Average	SD (+)
0	0	0	0	0	0
1	0.1 16	0.1 16	0.1 1 6	0. 1 16	0
2	0.25	0.25 I	0.251	0.250667	0.0005
4	0.468	0.468	0.468	0.468	0
6	0.665	0.655	0.665	0.661667	0.005
8	0.856	0.856	0.856	0.856	0

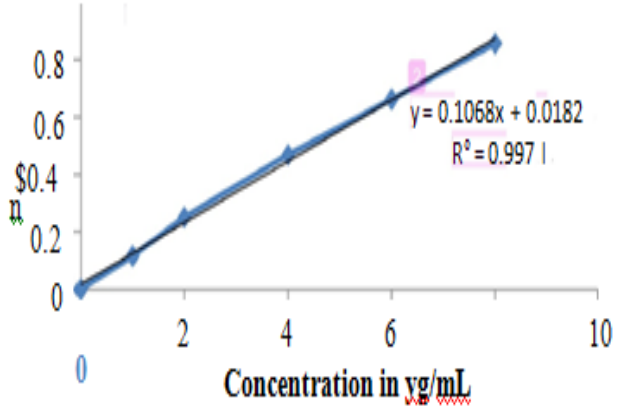

Fig 3: Calibration curve in organic solvent

Preparation of Stock Solution in Phosphate Buffer pH:

100yg/ml standard stock solution was prepared by transferring 10 mg Diclofenac in 100 ml volumetric flask, 30 ml of 0.1 M NaOH was added and the mixture was sonicated until the drug was completely dissolved and the final volume was made up by phosphate buffer pH 6.4

From the above standard stock solution, fresh aliquots were pipette out and made suitable delusion with phosphate buffer pH: 6.4, with the concentration range 2 to 1 6 kg/ml. The solution was scanned under IV range 200-400 nm wavelength and the sharp peak was obtained at 275 nm. Calibration curve showing absorbance on Y -axis and concentration on X-axis.

Preparation of calibration curve

Table 7: Absorbance of Diclofenac in Phosphate Buffer pH: *6*

Concentration	Absorbance			
	A1	A2	A3	Average
0	0	0	0	0
2	0.139	0.139	0.139	0.139
4	0.253	0.254	0.254	0.253667
6	0.358	0.358	0.358	0.358
fi	0.475	0.475	0.475	0.475
10	0.568	0.567	0.567	0.567333
12	0.69	0.69	0.69	0.69
14	0.797	0.797	0.797	0.797
16	0.903	0.903	0.903	0.903

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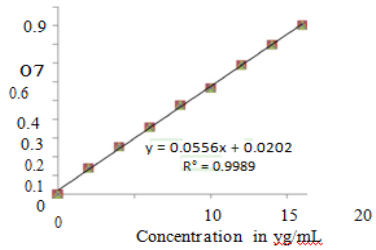

Fig. 4: Calibration Curve in Phosphate buffer

IR study confirms that the given API drug is pure and thus conclude that the given compound peak and reference matches by 99.98°/c, hence we say that the given compound was pure, studies were conducted in the range of 400 — 4000cm'.

Table 8: Formulation design of Diclofenac

Ingredients	F1	F2	F3	F4	FS	F6
Diclofenac	0.1	0.5	0.4	0.94	0.05	0.1
Sodium	250.12	250.12	250.01	250.31	250.43	250.32
Pectin	125.23	150.2	200.12	250.25	300.21	325.23
Calcium	80.32	90.2	100.34	110.23	120.25	130.32
Methanol:	QS	QS	QS	QS	QS	QS

Table 9: In-Vitro Drug release Studies of Optimized Formulation F4 in pH fit

Sr. No.	Time in hr	°/e Cumulative drug release				
		Vessel I	Vessel 2	Vessel 3	Average	SD (+)
1	0	0	0	0	0	0
2	1	47.4	43.37	43.3714	44.7 I	2.3259
3	2	55.66	56.75	49.3267	53.9 I	4.01 I
4	3	63.57	66.78	61 .0279	63.79	2.88
5	4	67.92	72.86	67.0784	69.28	3.12
6	5	77.23	78.97	76.0178	77.41	I .48
7	6	79.94	79.98	77.0048	78.97	I .7082
8	7	81.52	82.70	82.5663	82.26	0.64
9	8	84.24	86.00	91 .585 I	87.28	3.83
10	9	100.13	100.18	100.08	100.13	0.052
11	10	100.67	100.72	100.619	100.67	0.05

Conclusion

Formulation and evaluation of polymeric microspheres of diclofenac were done where identification and some of the analytical studies of diclofenac was carried out. Various physiochemical characteristics were studied for melting point (283 -2S5'C), Hausner's ratio, bulk density, tapped density, compressibility index, and angle of repose.

Ionotropic gelation method was used to formulate a polymeric microsphere of diclofenac with the help of sodium alginate as a cross linker and pectin as a polymer for controlled release of drugs. Calcium chloride was used as a suspending agent in agglomerating solid dispersion.

DSC and IR scan of drug and polymer samples used shows the purity and proof of no internal reactions between drug and other excipients as shown in appendices. In vitro drug release was studied and plotted for pH 6.4 and 6.8.

The formulation was optimized for different ratios of pectin and calcium chloride, the best-optimized formulation (F4) was again taken in triplicate for in-vitro drug release studies and is applied to the best fit model, this graph represents the I "model of in vitro drug release.

For in vivo studies, sodium alginate microspheres of diclofenac was prepared by ionotropic gelation method and were then successful radio labeled using reduced technetium-99rn with the labeling efficacy of more than 97%. Microspheres were then encapsulated in an enteric- coated capsule for colon delivery and were given orally to a white male rabbit of wt. 3.5kg.Different scans of rabbits were taken by gamma cameras through SPECT machine. Four Images were taken for different time hours, thus showing the distribution of the drug in the colon with time and hence scintigraphy confirms the drug deposition and distribution in colon marked in images with help of tracer.

After conducting these studies, that F4 is the best formulation among all six formulations because it releases the maximum drug, this indicates that F4 formulation will lead to bioavailability and prolonged drug release. The preparation of solid dispersion by the use of polymer results in good binding of dug and also increases the time of the drug in a body ultimately decreasing the side effects and increases the bioavailability with better patient compliance.

Hence, the radio labelled rnicrospheres of diclofenac were prepared and were implemented on anirilals in a scintigraphic process held in mas (Institute of Nuclear Medicine and Allied Sciences), DRDO(Defense Research Development Organization), New Delhi.

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