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DEVELOPMENT AND EVALUATION OF MICROSPONGE DRUG DELIVERY SYSTEM OF INDOMETHACIN

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ABSTRACT

In the present study controlled release formulation of Indomethacin microsponges were prepared by using Carbopol 940, PVA. Microsponges were prepared by Quasi emulsion solvent diffusion method by changing drug polymer ratio (1:0.5-1:4) and process was optimized. Microsponges were evaluated by micromeritic properties, drug content, encapsulation efficiency, and particle size. Characterization of Indomethacin microsponges were done by FT-IR spectroscopy,. In-vitro dissolution study indicated that the release of Indomethacin varied according to the concentration of matrix forming polymer, drug release mechanism was found to be super case II transport Therefore, Indomethacin microsponges prepared in thus study are promising as being more useful than conventional formulation intherapy.

Keywords: Indomethacin,carbapol940, PVA,FT-IR.

INTRODUCTION

The Microsponge Delivery System (MDS) is a patented polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface through which active ingredient are released in a controlled manner. The size of the microsponge‟s ranges from 5-300µm in diameter and a typical 25µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 feet in length, providing a total pore volume of about 1ml/g for extensive drug retention. The surface can be varied from 20 to 500 m2/g and pore volume range from 0.1 to 0.3cm3/g. This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent. 8, 9 The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc.10 This Company developed a large number of variations of the procedures and those are applied to the cosmetic as well as over-the-counter (OTC) and prescription pharmaceutical products. At the current time, this interesting technology has been licensed to Cardinal Health, Inc., for use in topical products.

Microsponges offers, enhanced product performance; extended release; reduced irritation and hence improved patient compliance; improved product elegancy; oil control: It can absorb oil up to 6 times its weight without drying; improved formulation flexibility; improved thermal, physical, and chemical stability; flexibility to develop novel product forms; These are also non-irritating, non-mutagenic, non-allergenic and non-toxic.

The MDS has advantages over other technologies like microencapsulation and liposomes. Microcapsules usually control release of the actives. Liposomes suffer from lower payload, difficult formulation, limited chemical stability and microbial instability. Similarly ointments are often aesthetically unappealing, greasy, sticky etc. They also require high concentration of the active ingredient for effective therapy.

MATERIALS AND METHODS

Materials: Indomethacin was procured from Dr. Reddyslabs,Hyderabad.Carbopol940,Polyvinyl alcohol (PVA) Ethanol and other excipients were procured from spectrum pharma research solutions,Hyderabad.

Method of Preparation of Microsponges: Microsponges of Indomethacin and Carbopol 940 was prepared by quasi-emulsion solvent diffusion method according to the formula given in table , the process involved formation of quasi-emulsion of two different phases i.e. internal phase and external phase similar to emulsions. Table gives the detailed information about the prepared formulations.

Steps involved in preparation:

1. The internal phase of drug-polymer solution (1: different ratio) and tri ethyl citrate made in a volatile solvent dichloromethane (10 ml).
2. And then it was added to external phase comprising the aqueous 5% (5 mg/100 ml water) polyvinyl alcohol (PVA) solution with vigorous stirring.
3. Glycerol (1-2 ml), which was added at an adequate amount in order to facilitate plasticity. Stirring lead to the formation of discrete emulsion globules called quasiemulsion globules.
4. The stirring was continued upto 6 hrs till the insoluble, rigid microparticles i.e. microsponges is formed.
5. Then it was filtered to separate the microsponges
6. The microsponges were then dried in an air heated oven.

EVALUATION OF FORMULATIONS:

Drug excipient compatibility study: The drug and excipient compatibility was observed using Fourier Transform – Infra Red spectroscopy (FT-IR). The FT-IR spectra obtained from Bruker FT-IR Germany (Alpha T) was utilized in determining any possible interaction between the pure drug and the excipients in the solid state. The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about $8t/in^2$. The spectra were recorded over the wave number of 8000 to $400cm^{-1}$.

Preparation of Standard Calibration Curve of indomethacin in 6.8 PH Buffer: Accurately weighed 10mg Indomethacin was dissolved in sufficient methanol taken in a clean 10ml volumetric flask. The volume was made up to 10ml with 6.8 ph buffer which gives a concentration of 1000µg/ml. From this standard solution, 1ml was pipette out in 10ml volumetric flask and volume was made up to 10ml using 6.8 ph buffer to obtain a concentration of 100µg/ml. From the above stock solution, aliquots of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 ml each was transferred to a separate 10ml volumetric flask and solution was made up to 10ml using 6.8 ph buffer to obtain a concentration of 2, 4, 6, 8,10 and 12µg/ml respectively. The absorbance of each solution was measured at 318 nm.

Evaluation of Preformulation parameters

i. Angle of repose.
ii. Determination of Bulk Density and Tapped Density
iii. Hausner's Ratio
iv. Compressibility index (Carr's Index)

Drug content uniformity: 10 mg of each formulation was taken and dissolved in 10 ml isotonic solution and kept overnight. 10 mg (similar as in formulation) of drug was taken and dilution was made to 10 µg/ml. The dilutions were filtered and analyzed using UV for their content uniformity. The absorbance of the formulations were read using one cm cell in a UV-Vis spectrophotometer. The instrument was set at drugs wavelength (nm). The drug content in each formulation was calculated based on the absorbance values of known standard solutions.

Percentage yield: It is calculated to know about the efficiency of any method, thus it helps in selection of appropriate method of production. After the preparation of formulations the Practical yield was calculated as Microsponges recovered from each preparation in relation to the sum of starting material (Theoretical yield). It can be calculated using following formula.

Percentageyield=Practicalyield/Theoretical yield (drug + polymer)X100.

Scanning electron microscopy: The morphological features of prepared microsponges are observed by scanning electron microscopy at different magnifications.

Particle size and shape: Average particle size and shape of the formulated microspongess was determined by using Malvern Zetasizer ZS using water as dispersions medium. The sample was scanned 100 times for determination of particle size.

Dissolution study: Dissolution is pharmaceutically defined as the rate of mass transfer from a solid

surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. It is a dynamic property that changes with time and explains the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent. The test determines the time required for formulation to release percentage of drug under specified conditions.

Dissolution Parameters

Medium : 900ml, 6.8ph buffer
Apparatus : Paddle (USP-I)
RPM : 100
Temperature : 37^{o} C±0.5
Time Points : 1,2,4,6,8,10,12, hr
Procedure:

For the oral dosage forms the in vitro dissolution study must be conducted in the dissolution medium which simulate the in-vivo conditions (actual physiological conditions). The in vitro drug release studies for the prepared formulation were conducted for a period of 12 hrs using an Electro lab model dissolution tester USP Type-1 apparatus (rotating paddle) set at 100 rpm and a temperature of 37± 0.5°C formulation was placed in the 900ml of the medium. At specified intervals 10ml samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant. The absorbance of the sample solution was analyzed at 318 nm for the presence of model drug, using a UV-visible spectrophotometer.

3. Stability Studies:

In the present study optimized formulation was selected for the study and formulations were packed in amber-colored bottles tightly plugged with cotton and capped. They were exposed to 40oC temp and 75% RH for 30 days. At regular intervals, the tablets were taken in 100 ml of pH 6.8 buffer and were shaken for 1 hr. The resultant solutions were filtered, properly dilutedand estimated spectrophotometrically by keeping pH 6.8 buffer as blank. % drug remained undecomposed was checked.

RESULTS AND DISCUSSION

Determination of indomethacin λ-max: Determination of indomethacin λ-max was done in 6.8 ph buffer for accurate quantitative assessment of drug dissolution rate. The indomethacin peak value is 318.

The linearity was found to be in the range of 2-12 µg/ml in 6.8 ph buffer. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

The solubility studies were conducted in various buffers we can say that 6.8 ph buffer has more solubility when compared to other buffer solutions.

FTIR STUDIES: It indicates that the drug was intact and has not reacted with the excipients used in the formulation and hence they are compatible. Hence, it can be concluded that the drug is in free-state and can release easily from the polymeric network in the free form.

MICROMERITIC PROPERTIES OF PURE DRUG:

Table1 : Flow properties of model drug

Test	**Result**
Bulk density	0.38
Tapped density	0.45
Carr's index	15.55
Hausner's ratio	1.18
Angle of repose (θ)	23.64

Inference: From the recorded observations it was found that Carr's index of model drug was 15.55and Hausner's ratio was 1.18 indicating drug have good compressibility index. Angle of repose was found to be 23.64 indicating drug have Excellent flow properties.

The drug content was of Microsponge revealed that the formulation F5 have the Drug content greater i.e. 86.29 mg and after that the drug content is decreasing with increase in content of polymer due to improper carrying of drug by the polymer.

The percent yield of the formulated microsponges was found to be 54.65-86.65%.The optimized formulation(F5) shows 86.65% yield.

By performing the SEM analysis it was observed that the shape of the microsponges affects the surface area and surface area per unit weight of spherical microsponges. The irregular shape of the particles may affect dissolution rate present in dissolution environment.

By performing the particle size analysis, it is concluded that the formulation has the particle size varies with the concentration of polymer drug ratio. the optimized formulation shows average particle size of 34.9µm.

By comparing the dissolution studies we can say that **F5** formulation shows 98.26% of drug release at the end of 12hours. so F5 Formulation is considered as the optimized formulation. Further drug release kinetics were performed for the optimized formulation.

The drug release from the microsponges were explained by the using mathematical model equations such as zero order, first order methods, higuchi and peppas plots. Based on the regression values it was concluded that the optimized formulation **F5**, followed zero order release where the regression

value was found to be 0.990, The mechanism of drug release is further confirmed by the korsmeyer and peppas plot.

The 'n' value is 1.235 for the optimised formulation(F5) i.e., n value was > 0.89 indicates Super case II transport.

The stability studies were done as per the ICH guidelines and the results compared to the optimized formulation . There was not much difference in the *in-vitro* release rates.

CONCLUSION

The Microsponges were prepared by quasi emulsion method and was evaluated for its different parameters which revealed many interesting results for efficient preparation of the microsponges. The formulation F5 have better results than other eight formulations. F5 have its particle size 34.9±1.05µm, percentage yield 86.65%, Drug content 86.29 mg, drug release Release 98.26% in 12 hour, all these parameters are in optimized range for preparing a extended release dosage form so showing itself as an optimized formulation in this project work.

FTIR spectroscopy analyses indicated the chemically stable, amorphous nature of the drug in these microsponges. SEM photographs revealed the spherical nature of the microsponges in all variations. With the revealed results by different evaluation parameters, it is concluded that microsponges drug delivery system has become highly competitive and rapidly evolving technology and more and more research are carrying out to optimize cost-effectiveness and efficacy of the therapy. It is a unique technology for the controlled release of topical agents and consists of microporous beads loaded with active agent and also use for oral as well as biopharmaceutical drug delivery.

Table2..Formulation table of Indomethacin loaded microsponges

S.NO	Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Indomethacin	1	1	1	1	1	1	1	1	1
2	Carbopol 940	0.5	0.75	1	1.5	2	2.5	3	3.5	4
3	Polyvinyl alcohol (PVA)	500	500	500	500	500	500	500	500	500
4	Ethanol	10	10	10	10	10	10	10	10	10
5	Purified Water	100	100	100	100	100	100	100	100	100
6	Drug : Polymer ratio	1:0.5	1:0.75	1:1	1:1.5	1:2	1:2.5	1:3	1:3.5	1:4

TABLE:3.Percent yield, particle size and drug content of microsponges:

S.NO	Formulation code	Particle size (µm)	Percent yield In %	Drug content %
1	F1	36.8±0.03	59.23	52.36
2	F2	38.5±1.04	62.03	56.45
3	F3	34.9±0.09	73.65	73.25
4	F4	31.9±0.02	65.98	79.93
5	F5	34.9±1.05	86.65	86.29
6	F6	32.6±0.06	82.35	80.24
7	F7	39.8±0.04	54.65	79.24
8	F8	41.9±0.07	60.12	75.63
9	F9	45.6±1.04	55.69	71.26

Table:4 In-Vitro Release Profile of formulations (F1-F9):-

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	31.28	28.21	25.96	22.12	16.39	12.43	11.02	9.62	6.24
2	49.89	36.94	32.22	32.16	22.81	18.24	14.21	12.65	11.82
3	66.29	48.29	44.82	46.04	30.24	24.21	18.21	19.21	16.21
4	79.23	57.32	52.32	52.73	36.06	29.35	21.23	22.12	19.82
5	89.28	64.82	59.28	59.02	41.12	34.62	24.02	27.06	24.42
6	98.24	79.52	69.26	69.97	53.89	41.36	28.02	38.75	32.38
7		86.66	78.21	76.37	61.25	49.67	35.81	49.74	38.81
8		99.64	84.26	84.47	74.11	54.33	46.8	58.51	42.28
9			92.58	90.23	82.97	62.11	51.26	67.16	56.26
10			98.42	99.19	88.56	70.86	59.16	74.55	69.16
11					94.82	79.74	70.91	82.45	72.91
12					98.26	84.86	86.72	80.24	78.72

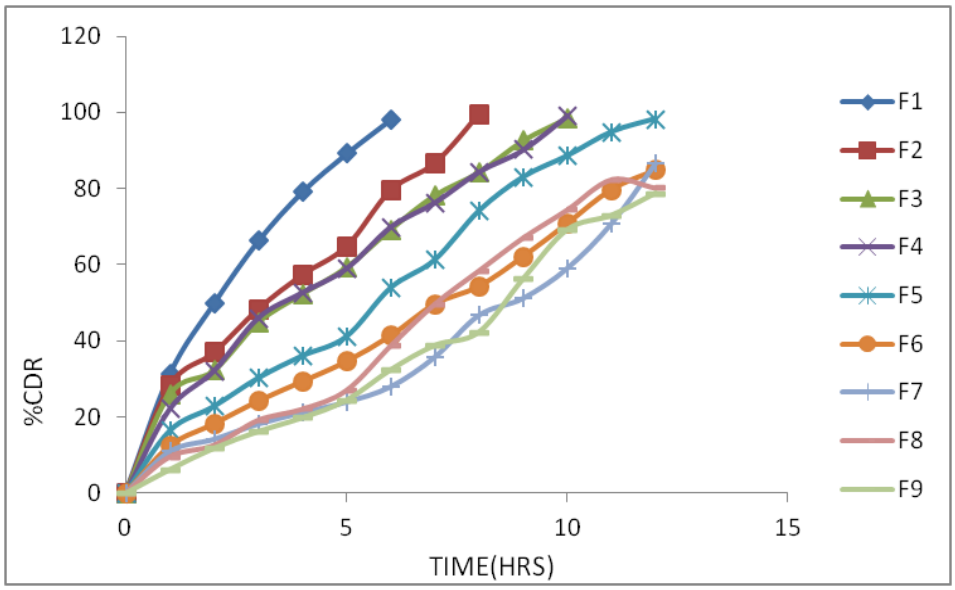

FIG:1. In Vitro drug release of formulations F1-F9.

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