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Original Article

Design and In-Vitro Characterization of Betamethasone Microsponge Loaded Topical Gel

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ABSTRACT

The aim of present study was to formulate and characterize the betamethasone microsponges loaded in to a topical gel for anti -inflammatory action. Here the controlled release microsponges were prepared by Quassi emulsion solvent diffusion method by varying concentrations of drug. The formulated microsponges were evaluated for morphology, drug excipient compatibility, encapsulation efficiency and in-vitro drug release. The prepared microsponges were incorporated in to a gel and the final gel was also evaluated for pH and invitro release. The invitro drug release of microsponges was found to be 77%. The SEM results have shown that the prepared microsponges were spherical and contain pores. FTIR studies revealed absence of incompatibility among drug, excipients and optimized formulation. The pH of gel was found to be 6.8 which suit the skin and the release was found to be 73%. The microsponges of betamethasone were successfully prepared evaluated and loaded in to a gel.

Key Words: Eudragit RS100; Betamethasone; Microsponges; Quassi emulsion solvent diffusion method, In-vitro release.

1. INTRODUCTION

Microsponges are polymeric delivery systems composed of porous microspheres of inert polymer that can entrap active ingredients and control their delivery rate. They are tiny true sponge like spherical particles that consist of myriad of interconnecting voids within a non-collapsible structure with large porous surface. The size of these microsponges can be varied, usually from 5 to 300 µm in diameter depending on the degree of smoothness [1]. By optimizing formulation parameters

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such as drug : polymer ratio and agitation/ stirring rate it might be possible to manufacture microsponge bead is of 25µm sized spheres which can have up to 250,000 pores and an average internal pore structure equivalent to 10 feet in length and average pore volume of about 1ml/g [2]. The surface can be varied from 0.1 to 500m^2/g and pore volume range from 0.1 to 0.3cm^2/g. This result is a large reservoir within each microsponge, which can be loaded with active agent up to its own weight. Since bacteria cannot penetrate a pore of this size, the beads once manufactured, remain sterile and do not require a preservative, once made they are very hard. They do not melt or dissolve and are stable at extremes of pH and up to 130ºC. The microsponges behave like a reservoir of the active ingredients. These can potentially be used for the controlled delivery of large variety of substances such as fragrances, emollients, sunscreens, anti-inflammatory, anti-fungal, antimicrobial agents. This entrapped active agent can be incorporated into many product forms, such as creams, gels, lotions, ointments, powders, soaps, tablets [3].A well known method for the encapsulation of hydrophobic drug within the hydrophobic polymer is solvent diffusion method [4]. The topical dosage formulation of betamethasone will help in the protection of drug from first pass effect i.e., presystematic degradation of drug in liver [5, 6, 7].Hence in present work an attempt was made to develop controlled release microsponges of betamethasone using synthetic polymer to minimize the frequent dosing, improve pharmacological effect and to improve patient compliance [8, 9].

Betamethasone is a steroidal anti-inflammatory drug which is used for the analgesic and anti inflammatory activity. The betamethasone is a synthetic corticosteroid which mimics the action of cortisol, the naturally occurring corticosteroid, which has the potent anti inflammatory action.

2. MATERIALS AND METHOD

Btamethasone was obtained as a gift sample from gsk, Eudragit RS 100, Dichloromethane, Ethanol,Polyvinyl alcohol, Carbopol, Triethanolamine were obtained from S.D.Fine chemicals, Mumbai.

Preparation of Betamethasone Microsponges

Microsponges were prepared by Quassi emulsion solvent diffusion method. In this method there were two phases i.e., internal phase consisted of drug (betamethasone), polymer (Eudragit RS100), solvent (Ethanol and dichloromethane in 1:1 ratio) and external phase consisted emulsifier (polyvinyl alcohol 0.5%w/v) and water. To prepare the inner organic phase, polymer was dissolved in solvent and then the drug was added to the solution and dissolved under ultrasonication. Then the inner phase was poured into the polyvinyl alcohol solution in water (outer phase). After 3hrs of stirring, the mixture was filtered to separate the microsponges and then obtained product was dried in air heated oven at 40^0C for 4hours.the composition of betamethasone microsponge is given in table:1

Table 1: Composition of betamethasone microsponges

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Betamethasone (mg)	100	100	100	100	100	100	100	100	100	100
EudragitRS100 (mg)	100	80	70	60	50	45	40	25	30	35
Ethanol(ml)	5	5	5	5	5	5	5	5	5	5
Dichloromethane (ml)	5	5	5	5	5	5	5	5	5	5
PVA(gms)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Distilled water(ml)	50	50	50	50	50	50	50	50	50	50

Drug –Excipent Compatibility studies

Infraredspectroscopy was performed to observe if any interactions were present between the drug and the excipient. The spectrum was recorded between 4000-400 cm^{-1} wavelength. The procedure consisted of finely grounding the sample (Drug alone, mixture of drug and Excepients, optimized formulation) along with the KBR. The finely grounded powder was then introduced in to a stainless steel die and was

compressed between polished steel anvils at a pressure of about 8t/in^2 to obtain a thin pellet. The pellet was placed in a light path and the spectrum was observed.

Evaluation of microsponges

Surface morphology of microsponges :

For morphology and surface characteristics, prepared microsponges were coated with gold-palladium under an argon atmosphere at room temperature and then the surface morphology of microsponges was studied by scanning electron microscopy.

Determination of percentage yield:

The production yield of the microsponges was determined by calculation accurately the initial weight of the raw materials and the weight of the microsponge obtained,

Production yield =(Wp/Wt) X 100

Where,

Wp =Practical mass of microsponges

Wt=Theoretical mass (polymer + drug)

Determination of encapsulation efficiency

10mg powder of the microsponge formulation was weighed and dissolved in 10ml of methanol under ultrasonication for 20min at 25^{0}C.then this sample was filtered and analysed at 242nm.

%Encapsulation efficiency = (A/T) x 100

A = Actual amount of drug present in weighed quantity of microsponges

T = Theoretical amount of drug present in microsponges.

Particle size analysis

Particlesize analysis was performed on microsponge formulation by optical microscope.

In-vitro release studies of Microsponges

Diffusion studies were performed using a artificial cell membrane, which was attached to one end of a frenz diffusion cell and the cell was placed in to a beaker containing the receptor medium(7.4pH buffer), such that the membrane just resides above the medium. From the other end of cell the weighed amount of microsponges were placed inside the cell, on the membrane. Then a magnetic bead was placed in the receptor medium and at RPM100 the bead was allowed to rotate on a magnetic stirrer. Then at regular intervals up to 8hours the sample was withdrawn from the receptor medium and drawn amount was replaced with the buffer. The drawn samples were analyzed to evaluate drug release at 242nm by using a double beam spectrophotometer.

Preparation of gel formulation

Carbopol of 1.5 gms was taken and dissolved in 100ml of water and left for the formation of gel overnight then the betamethasone microsponges were dispersed in the gel evenly.

Table 2: Composition of microsponge loaded gel

Components	MG1	MG2
Betamethasone microsponges	Eq. to 10mg of drug	Eq. to 10mg of drug
Carbopol(gms)	1	1.5
Triethanolamine(ml)	1	1
Distilled water(ml)	100	100

Evaluation of gel loaded with microsponges

pH Determination of gel

The pH of gel was measured using a digital pH meter. The weighed amount of gel was taken and dispersed in 25ml of purified water. Then the pH of dispersion was measured using pH meter, which was previously calibrated.

In-vitro drug release studies of gel

Diffusion studies were performed using artificial cell membrane, which was attached to one end of a Franz diffusion cell and the cell was placed in to a beaker containing the receptor medium(7.4pH buffer), such that the membrane just resides above the medium. From the other end of cell the weighed amount of microsponge loaded gel was placed inside the cell, on the membrane. Then a magnetic bead was placed in the receptor medium and at 100rpm the bead was allowed

to rotate on a magnetic stirrer. Then at regular intervals, up to 8hours 1ml sample was withdrawn from the receptor medium and drawn amount was replaced with the buffer. The drawn samples were analyzed to evaluate drug release at 242nm by using a double beam spectrophotometer.

3. RESULTS AND DISCUSSIONS

Compatibility studies

FT-IR spectra were recorded to observe the compatibility of the drug with the excipients.FT-IR of drug and optimized formulation were examined. In FT-IR spectra of Betamethasone powder, characteristic O-H stretching band at 3345 cm^{-1},C=O stretching at 1607 cm^{-1},C-O of phenol stretching at 1253 cm^{-1} were observed. These are the major peaks of the spectra of the drug. All these peaks were present in the spectra of optimized formulation and thus confirm that the drug did not interact with the excipients.

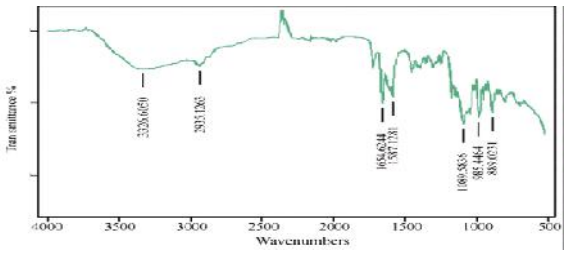

Fig 1: FT-IR spectra of Pure Betamethasone

Evaluation of Microsponges

Particle size and shape

The SEM photographs of microsponges are shown in the figure. Particle size analysis showed the particle size range from 1 to 80 µm and spherical in shape. Percentage of particles ranging in different sizes is shown in the table-3

Table 3: Particle size distribution of Betamethasone Microsponges

Range of particle size in micrometres	% no. of particles in F5	% no. of particles in F6	% no. of particles in F7	% no. of particles in F8
1-40	49.27	52.55	51.82	41.60
41-80	38.68	39.41	35.76	44.52
81-120	7.29	5.83	8.02	7.22
121-160	1.45	1.45	2.18	2.18
161-200	1.45	0	1.45	2.18
201-240	0.72	0.72	0.72	0.72
241-280	0	0	0	0.72
281-320	0.72	0	0	0.72

Production yield and encapsulation efficiency

The encapsulation efficiency and % yield increased up to a range with increase in the amount of drug and later they were found to be decreased due to decrease in the availability of the polymer to encapsulate the excess drug. The encapsulation efficiency and the production yield are shown in the table. The percentage yield of stable formulations F5 to F8 were from 87.23% to 69.23% and encapsulation efficiency was observed in the range between 55 to 64%.

Table 4: %yield and encapsulation efficiency

S.No	Microsponge formulations	% yield	Encapsulation efficiency%
1	F5	87.23	55
2	F6	88.69	64.6
3	F7	81.2	56.45
4	F8	69.23	58.20

In-vitro release studies

The in-vitro drug release was less in the beginning hours and the drug release gradually increased and it was observed that up to 8hours the complete drug was not released so it indicates that there was a controlled release of the drug. This indicates that the betamethasone microsponges release drug in a controlled manner. The release patterns of all the formulations are shown in the table:6, The optimized F7 formulation is showing 88.31%drug release in 9 hour.

Table 5: In-vitro release of Betamethasone microsponges

S.No	Time (hr)	% Cumulative Drug Release			
		F5	F6	F7	F8
1	0.5	1.93	1.16	1.38	5.07
2	1	3.42	4.95	4.92	9.81
3	2	13.26	7.65	11.71	20.06

4	3	22.22	20.94	39.25	29.81
5	4	36.24	35.55	44.95	39.73
6	5	44.33	39.61	55.84	48.48
7	6	51.1	49.92	66.3	55.56
8	7	65.34	60.57	77.63	64.31
9	8	82.22	76.76	88.31	71.22

Evaluation of GEL

pH determination of Microsponge Gel:

The formulated microsponge gel was tested for the pH using pH meter which showed the resultant pH as 6.8 which is suitable pH for a topical formulation.

Table 6: pH of Microsponge loaded gel

Formulation	pH
MG2	6.86

In-vitro release studies of GEL

The release of drug MG2 was observed to increase with the increase in time gradually up to 8 hours.

Table 7: Invitro release of Microsponge loaded gel

S.No	Time(hrs)	Cumulative % drug release of MG2
1	0.5	1.05
2	1	3.82
3	2	5.66
4	3	20.1
5	4	30.5
6	5	35.14
7	6	50.1
8	7	58.86
9	8	73.81

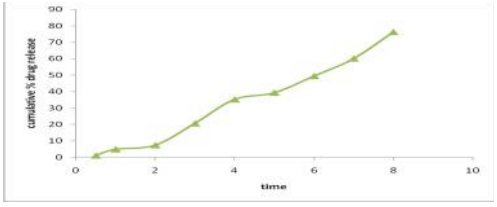

Fig 2: %Drug release graph of optimized formulation MG2

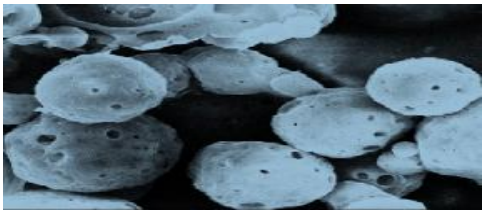

Fig 3: Scanning Electron Microscopy (SEM) of microsponges

4. CONCLUSION

Drug delivery via polymer systems has been proposed to be the prevailing in the type of controlled drug delivery devices both in present and future. For scientific as well as economic reasons, such delivery systems have potential advantage which include enhanced therapeutic response, predictable rate of release, extent of absorption and improved patient acceptance.

In the present work topical microsponge formulation of steroidal anti inflammatory drug has been developed. The study includes formulation and evaluation of betamethasone microsponges which are further incorporated in to gel for easier application of microsponges.

The idea to develop topical microsponges was to deliver the drug in a controlled manner and to prevent the drug from wear and tear of topical abrasions.

The ratio of drug to polymer was varied in the microsponge preparation and then the microsponges were evaluated for the encapsulation efficiency, particle size, size distribution and drug and excipient compatibility by FTIR and morphological study by SEM. The gel was formulated with different concentrations of Carbopol. The gel formulations were evaluated for the pH and invitro release.

SEM photographs revealed that the formulation is uniform and spherical.

Invitro drug release studies revealed that the optimized formulation released 76% of drug in a controlled manner.

By considering all the results, F6 was found to be the best formulation amongst all the microsponge formulations. This was selected for the gel formulation and gel was evaluated for the drug release and pH calculation.

Therefore it can be concluded that the betamethasone microsponges, prepared using Quassi emulsion solvent

diffusion method, loaded in to a gel can be used successfully for the topical anti inflammatory action.

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