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FORMULATION DEVELOPMENT AND EVALUATION OF BALSALAZIDE LOADED NANOSPONGES FOR IBD

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ABSTRACT

Colonic Drug Delivery Systems (CDDS) are especially advantageous for local treatment of inflammatory bowel diseases (IBD). Site-targeted drug release allows obtaining a high drug concentration in injured tissues and less systemic adverse effects, as consequence of less/null drug absorption in small intestine. This review focused on the reported contributions in the last four years to improve the effectiveness of treatments of inflammatory bowel diseases. The aim of the present research work was to develop sustained release nanosponges formulation of Balsalazide targeted to colon by using various pH dependent polymers. The maximum encapsulation efficiency was also found maximum in formulation F3 (89.78±0.45), select as optimized formulation for further evaluation. The surface charge of optimized formulation of nanosponges F-3 was found -20.2 and average particle size was found 52.74±1.05. The analytical characterization showed good purity of the drug. *In vitro* drug release showed a good release profile of prepared optimized-sponges formulation.

Key words: Balsalazide, Nanosponges, Formulation, Evaluation, IBD.

INTRODUCTION:

Nanotechnology is science of element and fabric that cope with particle length in nanometers. The word 'Nano' is derived from Latin word, which means dwarf (1nm=10µm). Nanomedicine offers with full-size monitoring, manage, repair, defense and improve human genetic device at molecular stage the usage of engineering nanostructures and nanodevices. Nanotechnology has received loads of attention with by no means-visible-before enthusiasm due to its budding capacity. It has provided satisfactory lined determination and cognizance treatment of ailment at molecular degree.

Nano-sponges are a singular method which attempt controlled drug shipping for topical use. Nano--spongesis an develop technology for

topical drug transport. Nano-sponges drug shipping machine is employed for the development of overall performance of topically carried out pills. Nano-sponges are small sponges with a length of approximately a pandemic, which can be full of a wide collection of medication. These tiny sponges can travel around the body till they encounter the exact goal site and stick on the surface and begin to discharge the drug in a managed and predicted way (Vyas and Khar, 2008). Nano-sponges have emerged as one of the maximum capable fields of existence technology due to their software in managed drug delivery (Selvamuthukumar *et al*., 2012). Nano-sponge era offers entrapment of components and is thought to make contributions towards compact aspect results, greater balance, improved elegance and more advantageous system elasticity (Selvamuthukumar *et al*., 2012). Nano-sponges are non-nerve-racking, non-mutagenic, nonallergenic and innocent (Renuka *et al*., 2011).

Nano-sponges are minute mesh-like systems that may revolutionise the curing of various illnesses and this generation is instances more treasured at turning in drugs for breast most cancers than traditional techniques (Nacht *et al.*, 1992; Trotta *et al.*, 2007). Nano-sponges are manufacturing up of minute molecule with few nanometers big cavities, in which a extensive variety of materials may be encapsulated. These particles are able to sporting each lipophilic and hydrophilic substances and of enhancing the solubility of weakly water soluble molecules (Jenny *et al*., 2011). Nano-sponges are encapsulating form of nano-particles which encapsulates the drug molecules within its center.[3] As compared to other nano-particles, nano-sponges are insoluble in water and organic solvents, porous, non-toxic and steady at excessive temperatures as much as 300°C (Renuka *et al*., 2011). These tiny sponges can journey across the body until they encounter the particular goal site and bond at the floor and provoke to discharge the drug in a prohibited and predictable way. Since the active drug can be launched at the precise goal site rather than circulating throughout the body it is going to be extra beneficial for a selected given dosage. Another critical function of those nano-sponges is their aqueous solubility which permits the usage of those systems correctly for drugs with low solubility. The nanosponges are solid in nature and may be define as oral, parenteral, topical or inhalational dosage bureaucracy. For oral organisation, those may be remoted in a model of excipients, diluents, lubricants and anticaking marketers which is suitable for the practise of tablets or tablets (Jenny *et al*., 2011). For parenteral administration, these can be it appears that evidently combined with

disinfected water, salty or other aqueous answers (Jenny *et al*., 2011). For topical management, they may be effectively incorporated into topical hydrogel (Leslie and Benet, 2007). The researchers at Vanderbilt University and Emory University newly reported on a controlled-release nano-particle drug delivery machine, which can be an advanced shipping approach for turning in anticancer therapies, along with direct injection into tumour site. This nano-particle float inside the body until they come upon the surface of a tumour cell, where they adhere to the surface and begin freeing the drug in a controlled and predictable way (Longo *et al*., 2011).

Nanosponges are porous polymeric delivery systems that are small spherical particles with large porous surface. Nanosponges can significantly reduce the irritation of drugs without reducing their efficacy (Srinivas and Sreeja, 2007). The size of the nanospongs ranges from 250nm-1μm in diameter. Nanosponges are made up of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules.

Balsalazide disodium is delivered intact to the colon where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalamine, which is the therapeutically active portion of the molecule, and 4-aminobenzoyl-β-alanine. The recommended dose of 6.75 grams/day, for the treatment of active disease, provides 2.4 grams of free 5- aminosalicylic acid to the colon. The aim of the present research work was to develop sustained release nanosponges formulation of Balsalazide targeted to colon by using various pH dependent polymers.

Material and Methods

Preparation of Nanosponges

The nano-sponges containing Balsalazide were formulated by a method called the quasi-emulsion solvent diffusion (Srinivas and Sreeja, 2007). The accurately weighed amount of polymethyl-methacrylate (PMMA), Eudragit S-100 in different ratios with dibutyl phthalate (1% w/v) was dissolved in 10 mL of dichloromethane: methanol (50:50). Dibutyl phthalate was incorporated to increase the polymer plasticity. Balsalazide was dissolved in this mixture. At the next, 0.5-1.5% w/v solution with distilled water was prepared as dispersing media. The previously prepared solution of polymers and drug was added gradually in PVA solution and stirring was kept constant for 2 hours. After complete evaporation of solvent from polymer droplets, nano-sponges were

formed, which were centrifuged at 4000 rpm for collection and followed by 3 times washing. The solvent was slowly removed to form the nano-sponges. The aqueous suspension of nano-sponges was lyophilized and stored in a tightly sealed container until further analysis. The optimization of the formulation of balsalazide loaded nano-sponges was given in Table 1.

Table 1: Composition of nanosponges formulations

Components	Formulation code/amount					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Balsalazide (mg)	50	50	50	50	50	50
Eudragit S-100 (mg)	10	20	30	10	20	30
PMMA (mg)	10	10	10	20	20	20
PVA (%)	0.5	1.0	1.5	0.5	1.0	1.5
Dibutyl phthalate (%)	1	1	1	1	1	1
Dichloromethane: methanol (50:50) (ml)	10	10	10	10	10	10
Distilled water	20	20	20	20	20	20

Determination of production yield

The production yield of the nanosponges was determined by calculating the initial weight of the raw materials and the final weight of the nanosponges obtained (Pande et al., 2015). All the experiments were performed in triplicate and the mean of the each value was reported.

Actual drug content and encapsulation efficiency

The weighed amount of drug loaded nanosponges (100 mg) was suspended in 100 ml 7.2 pH Phosphate Buffer and subjected to intermittent stirring (Shoaib et al., 2018). The sample was filtered using 0.45_m membrane filter and analyzed at 480.0 nm against blank using UV spectrophotometer (Labindia, 3000+). All analyses were carried out in triplicate. The results of actual drug content and encapsulation efficacy are shown in Table 8.2.

Actual drug content (%) $= M_{act}/M_{ms} \times 100$

Encapsulation efficiency (%) $= M_{act}/M_{the} \times 100$

Where M_{act} is the actual drug content in nanosponges, M_{ms} is the total amount of the nanosponges and M_{the} is the amount of drug

added to the nanosponges. All analyses were carried out in triplicate (Kumar *et al*., 2018).

Surface charge and vesicle size

The Particle size and size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (SAIF RGPV Bhopal, Malvern Zetamaster, ZEM 5002, Malvern, UK). Zeta potential measurement of the nanosponges was located on the zeta potential that was determined according to Helmholtz–Smoluchowsky from their electrophoretic mobility. For measurement of zeta potential, a zetasizer was used with field strength of 20 V/cm on a large bore measures cell[12]. Samples were diluted with 0.9% NaCl adjusted to a conductivity of 50 lS/cm.

***In-vitro* release studies**

***In vitro* drug release in gastrointestinal fluids of different pH**

The prepared nanoparticles were evaluated for *in vitro* drug release. The drug release studies were carried out using USP I Basket type dissolution test apparatus (Aggarwal et al., 2016; Arvapally et al., 2017). The dissolution study was carried out in 900 ml dissolution medium which was stirred at 100 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows:

- *1st hour:* Simulated gastric fluid (SGF) of pH 1.2.
- *2nd and 3rd hour:* Mixture of simulated gastric and Intestinal fluid of pH 4.5.
- *4th to 5th hour:* Simulated intestinal fluid (SIF) of pH 6.8.
- *6th hour and onward:* SIF pH 7.2

A weighed quantity of formulation (equivalent to 30mg) was filled in capsule and kept in basket of dissolution apparatus with dissolution media (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 5ml by media. The samples withdrawn were assayed spectrophotometrically at 480.0 nm for percent of release Balsalazide using UV visible spectrophotometer. The release of Balsalazide was calculated with the help of Standard curve of Balsalazide.

RESULTS AND DISCUSSION

The actual drug content of prepared nanosponge's formulation F1, F2, F3, F4, F5 and F6 was found to be 89.12±0.12, 92.45±0.45, 98.23±0.43, 91.56±0.32, 94.56±0.21 and 91.32±0.45 respectively. The maximum drug content was found in formulation F3 (98.23±0.43). The Encapsulation efficiency of formulation F1, F2, F3, F4, F5, and F6 was

found 78.89±0.15, 79.89±0.12, 89.78±0.45, 84.56±0.23, 80.18±0.14 and 80.18±0.14. The maximum encapsulation efficiency was also found maximum in formulation F3 (89.78±0.45), select as optimized formulation for further evaluation. The surface charge of optimized formulation of nanosponges F-3 was found -20.2 and average particle size was found 52.74±1.05.

In vitro drug release from nanosponges was carried out using dissolution apparatus. The *in vitro* drug release data of the formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of formulation was maximum i.e 0.984 hence indicating drug release from formulations was found to follow Zero order of drug release kinetics. Maximum drug release from optimized formulation (F3) after 12 hrs.

Table 1: Result of actual drug content and encapsulation efficiency

Formulation code	Actual drug content (%)	Encapsulation efficiency (%)
F1	89.12±0.12	78.89±0.15
F2	92.45±0.45	79.89±0.12
F3	98.23±0.43	89.78±0.45
F4	91.56±0.32	84.56±0.23
F5	94.56±0.21	80.18±0.14
F6	91.32±0.45	84.74±0.25

Table 2: Characterization of Optimized formulation of nanosponges

Characterization	Average Particle size (nm)	% Encapsulation efficiency	Zeta Potential (mV)
F-3	52.74±1.05	84.56±00.23	-35.5±2.4

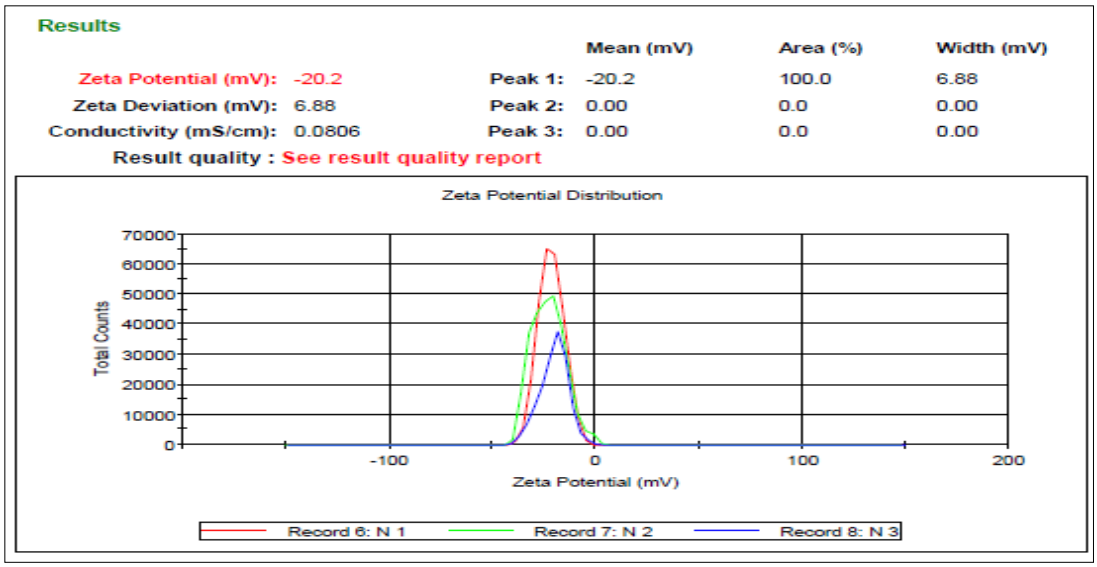

Figure 1: Graph of zeta potential

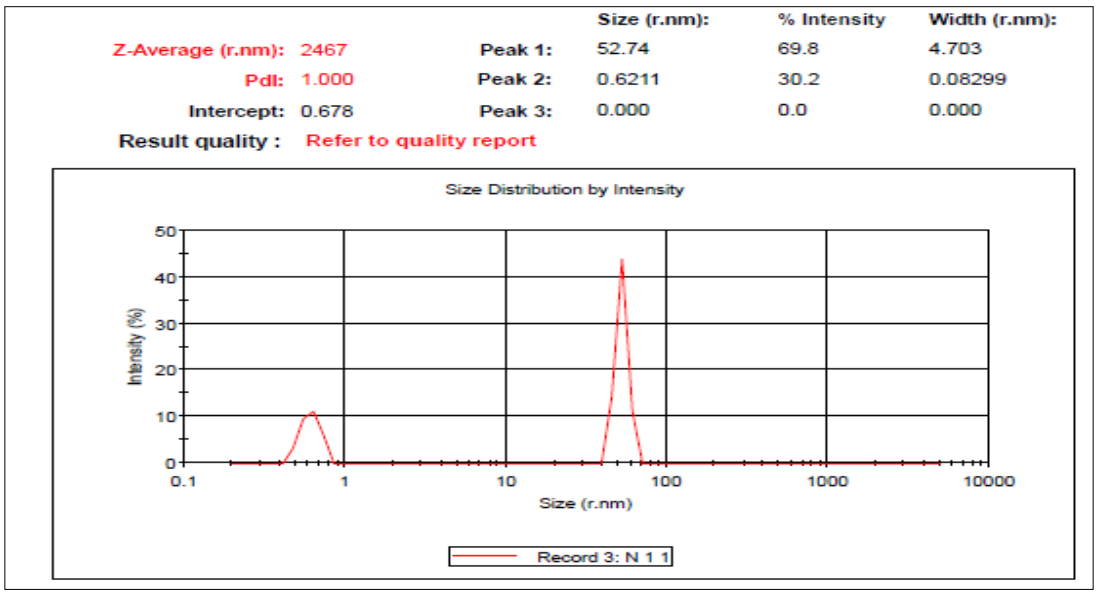

Figure 2: Graph of surface charge and vesicle size

Table 3: Cumulative % drug release of Balsalazide nanosponges at different pH

S. No.	Dissolution medium	Time (hrs)	% Cumulative drug Release
1	SGF (pH 1.2)	1	8.54
2		2	11.25
3	SIF (pH 7.2)	3	22.23
4		4	29.98
5		5	36.65
6		6	45.58
7		7	55.69
8		8	68.85
9		9	73.32
10		10	88.85
11		12	92.23

Table 4: *In vitro* drug release data for coated formulation

S. No.	Time (H)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.000	0.000	8.54	0.931	91.46	1.961
2	2	1.414	0.301	11.25	1.051	88.75	1.948
3	3	1.732	0.477	22.23	1.347	77.77	1.891
4	4	2.000	0.602	29.98	1.477	70.02	1.845
5	5	2.236	0.699	36.65	1.564	63.35	1.802
6	6	2.449	0.778	45.58	1.659	54.42	1.736
7	7	2.646	0.845	55.69	1.746	44.31	1.647
8	8	2.828	0.903	68.85	1.838	31.15	1.493
9	9	3.000	0.954	73.32	1.865	26.68	1.426
10	10	3.162	1.000	88.85	1.949	11.15	1.047
11	12	3.464	1.079	92.23	1.965	7.77	0.890

* Average of three determinations

Table 5: Regression analysis data of nanosponges formulation

Formulation	Zero order	First order	Pappas plot
F3	$R^2 = 0.984$	$R^2 = 0.899$	$R^2 = 0.979$

CONCLUSION

Nano-sponges based Balsalazide system was developed successfully by using a quasi-emulsion solvent diffusion method for prolonged transport of drugs for an extended period to decrease application frequency allied to the standard marketed formulation and to enhance bioavailability and safety. The analytical characterization showed good purity of the drug. *In vitro* drug release showed a good release profile of prepared optimized-sponges formulation.

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