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Formulation and Evaluation of Mesalamine Nanosphere Tablet

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ABSTRACT

Nanospheres are the particles having the size range between 10-200 nm in diameter. Nanospheres can be amorphous or crystalline in nature and also they have the ability to protect the drug from enzymatic and chemical degradation. For the preparation of standard calibration curve of Mesalamine with Phosphate buffer pH 6.8 and Absorbance of µg/ml solution was measured between 200-400nm by using Shimadzu 1601 UV/Vis double beam spectrophotometer. The Melting point of Mesalamine was determined using open capillary method. Infrared spectroscopy analysis of Mesalamine pure drug was performed by Fourier transfer infrared spectroscopy. Nanosphare containing Mesalamine were prepared using nanoprecipitation method. 200 mg of polymer (Eudragit RS and L) was dissolve in 50 ml water. Drug was dissolve in 20 ml of methanol. Both solution were mixed and add 50 ml of water and stirred for half an hour. Methanol and water was evaporated under reduced pressure using rotary flash evaporator until 10 ml of solution was remaining. Than this suspension was centrifuge at 15000 rpm at 4^0C for half an hour. The supernatant was discarded and remaining portion was washed with distilled water. The nano-sphares was dried over night at 60^0C and stored in desiccators. The surface morphology (roundness, smoothness, and formation of aggregates) and particle size was studied by scanning electron microscopy (SEM). Zeta potential of the best formulation (F4) was determined by zeta potential probe model DT- 300. Mesalamimne, Dextrose and Lactose were taken in required quantities mixed and granulating agent (Starch past) was added and passed through #40 sieves, then lubricant magnesium stearate and talc was added then compressed into tablets by rotary tablet punching machine. Then film coating is done by 6% w/v solution of Cellulose acetate Phthalate in isopropyl alcohol using 2% tween-80 as plasticizer in coating pan. The weight of tablet was kept constant for all formulations. Nanosphare tablet formulation F-2 Showed maximum drug (97.75%) released and formulation F-4 showed 92.58% drug release. The *In-vitro* drug released study result showed that formulation F-2 96.58% drug was released after 17 hours which is highest drug release amongst all other tablet formulation.

Keywords: Nanospheres; Mesalamine; Nanoprecipitation; Colon Targeted Drug Delivery

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1. INTRODUCTION:

1.1 Nanosphere

Nanoparticles can be divided into two main families: nanospheres, which have a homogeneous structure in the whole particle, and nanocapsules, which exhibit a typical core-shell structure. Nanospheres are the particles having the size range between 10-200 nm in diameter. Nanospheres can be amorphous or crystalline in nature and also they have the ability to protect the drug from enzymatic and chemical degradation. It has been shown that the hydrophobic surfaces of these particles are highly susceptible to opsonization and clearance by the reticulo endothelial system. The tiny capsule of drug store house is called vesicles and the solid skeleton structure is called Nanospheres. Biodegradable Nanospheres include albumin Nanospheres, modified starch Nanospheres, gelatin Nanospheres, polypropylene dextran Nanospheres and polylactic acid Nanospheres. In addition there are two more types of Nanospheres, immune Nanospheres and magnetic Nanospheres. Immuno-magnetic nanospheres can be prepared by combining the above two kinds of nanospheres, which could significantly improve its targeting.

1.2 Method of preparation of Nanospheres

There are various types of method by which Nanospheres are prepared.

- Polymerization (Emulsification polymerization)
- Solvent Evaporation.
- Solvent displacement technique.
- Phase inversion temperature methods.

2. MATERIAL AND METHODS

2.1 Preformulation studies of Mesalamine pure drug

2.1.1 Preparation of standard calibration curve of Mesalamine

10 mg of drug was dissolved in Phosphate buffer pH 6.8 and final volume was making up to 100 ml in 100 ml volumetric flask. The stock solution concentration was 100 mcg/ml obtained. It was diluted with Phosphate buffer pH 6.8 to obtain solution in Concentration range10 to 60 µg/ml. Absorbance of µg/ml solution was measured between 200-400 nm by using Shimadzu 1601 UV/Vis double beam spectrophotometer.

2.1.2 Melting point determination

The Melting point of Mesalamine was determined using open capillary method. The capillary filled with drug powder was placed in Thiel's tube containing liquid paraffin. The tube was heated and the melting point of the drug powder was noted. The average of three values was considered as the melting point of drug.

2.1.3 FTIR Spectra of pure drug

Infrared spectroscopy analysis of Mesalamine pure drug was performed by Fourier transfer infrared spectroscopy.

2.2 Preparation of Nanosphare[2]

Nanosphare containing Mesalamine were prepared using nanoprecipitation method. 200 mg of polymer (Chitocan, Pectin) was dissolve in 50 ml water. Drug was dissolve in 20 ml of methanol. Both solution were mixed and add 50 ml of water and stirred for half an hour. Methanol and water was evaporated under reduced pressure using rotary flash evaporator until 10 Ml of solution was remaining. Than this suspension was centrifuge at 15000 rpm at 4^0C for half an hour. The supernatant was discarded and remaining portion was washed with distilled water. The Nanospheres was dried over night at 60^0C and stored in desiccators.

Table 1 Formulation table of Nanosphare

S. N.	Material	F-1	F-2	F-3	F-4
1	Mesalamine (mg)	500	500	500	500
2	Eudragite S 100 (mg)	250	500	-	-
3	Cellulose acetate Phthalate (mg)			250	500
4	Tween 80 (ml)	0.2	0.2	0.2	0.2
5	Methanol (ml)	20	20	20	20
6	Water (ml)	100	100	100	100

2.3 Evaluation of Nanosphare

2.3.1 Particle size, surface morphology and zeta potential[13]

The surface morphology (roundness, smoothness, and formation of aggregates) and particle size were studied by scanning electron microscopy (SEM). Zeta potential of the best formulation (F4) was determined by zeta potential probe model DT- 300.

2.3.2 Drug entrapment efficiency [13]

Drug content was determined by centrifugation method. The Nanosphare were redisperse by centrifugation in Phosphate buffer pH 6.8 at 15,000 rpm for 40 min at 25^0C to separate the free drug in the supernatant. Concentration of Mesalamine in the supernatant was determined by UV-Viss. spectrophotometyrically at 232 nm after suitable dilution.

2.3.3 Fourier Transform Infra-red Spectroscopy (FT-IR) analysis

The FT-IR spectra of pure Mesalamine Chitosan (F-2) Nanosphare were recorded to check drug polymer interaction and stability of drug.

2.3.4 *In -vitro* release studies[14]

In-vitro release studies were carried out by using dialysis tubes with an artificial membrane. Initial 3 hour the nanosphare of Mesalamine drug release study was conducted using 0.1 HCl as dissolution medium then the prepared Mesalamine Nanosphare and 10 ml of Phosphate buffer pH 6.8 was added to the dialysis tube and subjected todialysis by immersing the dialysis tube to the receptor compartment containing 250 ml of phosphate buffer pH 6.8.The medium in the receptor was agitated continuously using a magnetic stirrer a temperature was maintained at 37±1^0C. 5ml of sample of receptor compartment were taken at various intervals of time over a period of 24 h and each time fresh buffer was replaced. The amount of drug released was determined spectrometrically at 232 nm.

2.4 Formulation of Mesalamine Nanosphare Tablet[17]

Mesalamimne, Chitosan, Ethylcellulose, Dextrose and Lactose were taken in required quantities mixed and granulating agent (Starch past) was added and passed through #40 sieves, then lubricant magnesium stearate and talc was added then compressed into tablets by rotary tablet punching machine. Then film coating is done by 6% w/v solution of Cellulose acetate Phthalate in isopropyl alcohol using 2% tween-80 as plasticizer in coating pan. The weight of tablet was kept constant for all formulations. A minimum of 100 tablets were prepared for each batch.

Table 2 Polymer concentration of tablet formulation

Sr. no	Ingredient	F-1	F-2	F-3	F-4	F-5	F-6
1	Mesalamine Nanosphare	500	500	500	500	500	500
2	Eudragite RS	25	50	75	-	-	-
3	Eudragite L	-	-	-	25	50	75
4	Lactose	75	50	25	-	-	-
5	Dextrose	-	-	-	75	50	25
6	Talc	5	5	5	5	5	5
7	Magnesium Stearate	5	5	5	5	5	5
8	Starch past	qs	Qs	qs	qs	qs	qs

*All Quantities in milligram

2.5 Drug Excipient compatibility study

The interaction of the drug and the excipient was carried out by FTIR method to know the physiochemical interaction occur in the drug and excipient.The drug and excipients is taken in 1:5 ratios and placed in a vial and rubber stopper was placed on the vial and sealed properly for 6 month at $40^0C \pm 2^0C/75\%RH \pm 5\%RH$.

2.6 Precompressed Parameter

2.6.1 Bulk density[18,19]

A quantity of 10 g of powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 50 ml measuring cylinder. The bulk volume and mass of the powder was determined. The bulk density was calculated using following formula:Bulk density= Weight of granules/ Volume of granules

2.6.2 Tapped density[18,19]

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder and the mass of the blend was measured. The tapped density was calculated using the following formula:

Tapped density= Weight of granules/ Volume of granules after 100 tapping

2.6.3 Carrs Index[18,19]

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by Carr¡¦s index which is calculated as follows:

Carr's index (%) = Tapped Density – Bulk Density/Tapped DensityX 100

Where,BD = Bulk density, TD = Tapped density

Table 3 Standards for Carr's index

Carr's Index	Flow
5 – 15	Excellent
12 - 16	Good
18 – 21	Fair
23 – 35	Poor
35 – 38	Very poor
More than 40	Extremely poor

2.6.4 Hausners ratio[18,19]

Hausners ratio value is less than 1.25 indicates good flow and greater than 1.5 indicates poor flow property which was calculated by using following formula:

Hausnre's ratio = Tapped density/ Bulk density

Table 4 Standards for Hausner ratio

Hausner ratio	Flow
1.2 – 1.3	Excellent
1.3 – 1.4	Good
1.4 – 1.5	Fair
1.5 – 1.6	Poor

2.6.5 Angle of repose[18,19]

It is determined by allowing a powder to flow through a funnel and fall freely on to a surface. Further addition of powder is stopped as soon as the pile touches the tip of the funnel. A circle is drawn around the pile without disturbing it. The height and diameter of the resulting cone are measured. The same procedure is repeated three times and the average value is taken. Angle of repose is calculated by using the following Formula:

$\tan \theta = h/r$ Where, h = height of the powder cone; r = radius of the powder

Table 5 Standards for Angle of Repose

Average weight	% difference
130 mg or less	10
130 – 324 mg	7.5
324 mg and greater	5

2.6.6 Friability[9]

For each formulations, preweighed tablet samples (20 tablets) were placed on the ronche friabilator, the friabilator was rotated 25 RPM which is then operated for 100 revolutions for 4 minute. The tablets were then dusted and reweighed. Conventional compressed tablets that loose less than 1.0% of their weight are considered acceptable.

The % friability was then calculated by,%Friability = $(W_0 - W) / W_0 \times 100$

Where, F = friability W_0 = initial weight of the ten tablets W = final weight of the ten tablets

2.6.7 Hardness[9]

Tablet hardness of each formulation was determined using a Monsanto hardness tester. Results were calculated from the average results of six tablets.

2.6.8 Thickness[9]

Tablet thickness is determined using vernier calipers in triplicate.

2.6.9 Disintegration test[10]

The disintegration test was conducted by disintegration test apparatus. Introduce one tablet into each tube and add a disc to each tube. Suspend the assembly in the beaker containing the Phosphate buffer pH 6.8 and operate the apparatus for a specified period of time. The tablet passes the test if all tablets have disintegrated. If one or two tablets fail to disintegrate, repeat the test on 12 additional tablets, if 2 out of 18 tablet was fail to disintegrate after specific time the test is fail.

2.6.10 *In-vitro* drug release studies[11]

The study was conducted with six tablets for each formulation using USP type II dissolution apparatus and 900 ml of 0.1 N HCl (First 3 hour) and Phosphate buffer pH6.8 as a dissolution medium at a paddle rotating speed of 75 rpm. Aliquots of 5 ml were withdrawn at selected time intervals through auto sampler and filtered through 0.45 filter and the same volume of dissolution medium was used to replace dissolution medium in order to maintain sink conditions. The absorbance of aliquots was measured at 232 nm using a UVspectrophotometer after appropriate dilutions.

2.6.11 Stability Study

The stability study was carried out for optimized formulation as per ICH guidelines. The nanoparticle of the best formulation were placed in screw capped glass container and stored at ICH storage (40^{0}C±2^{0}C/75%RH±5%RH) condition for a period of 60 days. The samples were analyzed for physical appearance and for the drug content.

Table 6 ICH guidelines for stability study

Study	Storage condition	Time period
Long term	25^{0}C±2^{0}C/60%RH±5RH	12 month
Intermediate	30^{0}C±2^{0}C/65%RH±5%RH	6 month
Accelerated	40^{0}C±2^{0}C/75%RH±5%RH	6 month

3. RESULT AND DISCUSSION

3.1 Preformulation study of pure drug

3.1.1 Calibration curve of Mesalaminein Phosphate buffer pH 6.8

Phosphate buffer pH 6.8 was used for the preparation of Mesalamine concentration and absorption was measure by Shimadzu UV-1601 UV/Vis double beam spectrophotometer. The λ max of Mesalamine was found to be 232 nm. The result was showed in the table no. 8 and figure no. 1.

Table 7 Standard CC of Mesalamine in Phosphate buffer pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1	10	0.125	0.121	0.130	0.125
2	20	0.292	0.287	0.292	0.292
3	30	0.399	0.393	0.402	0.399
4	40	0.574	0.569	0.579	0.574
5	50	0.771	0.768	0.776	0.771
6	60	0.918	0.915	0.921	0.918
Correlation Co-efficient (R^2) = 0.9947 Absorbance (y) = 0.159$_x$ conc - 0.0445					

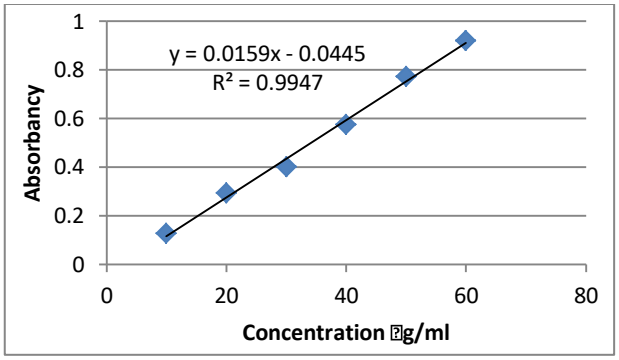


Figure1 Drug calibration curve in Phosphate buffer pH6.8

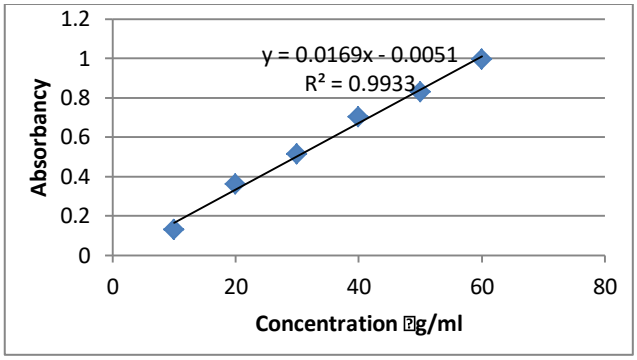


Figure 2 Drug calibration curve in 0.1 N HCl

3.1.2 Calibration curve of Mesalaminein 0.1 N HCl

Mesalamine concentration was prepared in 0.1 N HCland absorption were measure by Shimadzu-1601 UV/Vis double beam spectrophotometer. The λ max of Mesalamine was found to be 232 nm.

3.1.3 Melting point: The average melting point of pure drug is 283^{0}C which is complies with Stander melting point of drug.

Table 8 Melting point of pure drug

S. N.	Melting point (^{0}C)	Average Melting Point (^{0}C)
1	284	283
2	283	
3	283	

3.1.4 FTIR Spectra of pure drug

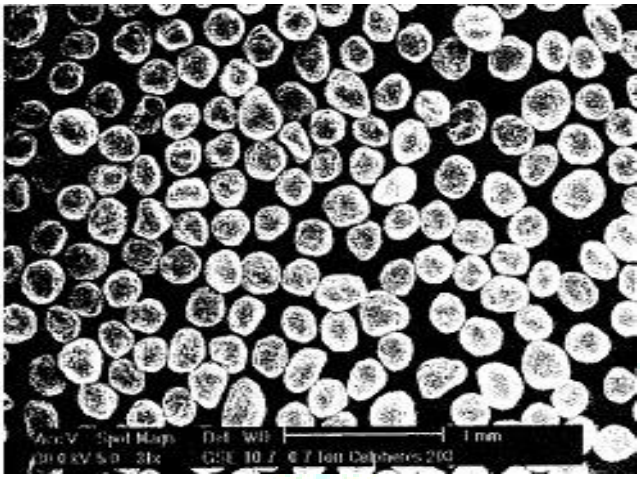
3.2 Drug excipient compatibility study of drug with Nanosphare polymer

Table 9 Physical observation after 6 month

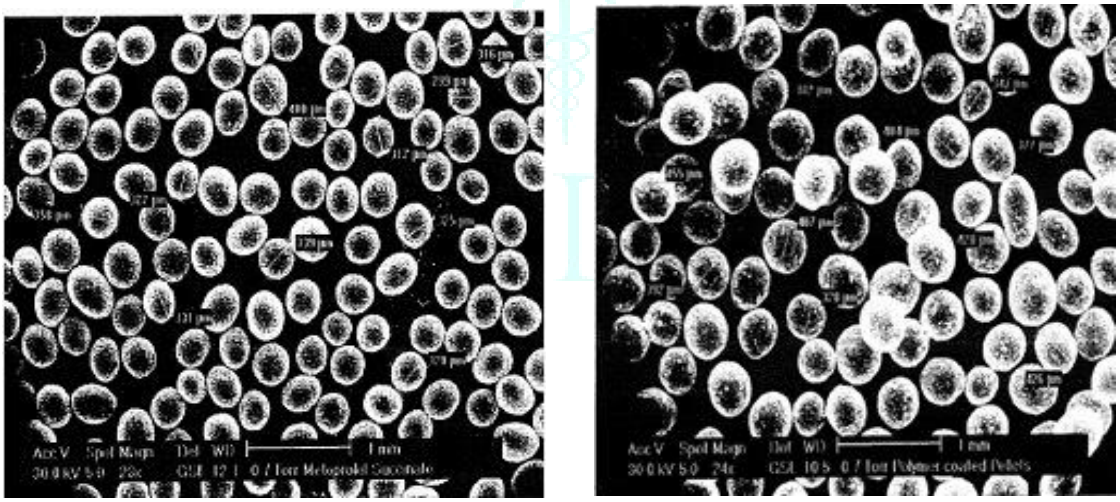
S. No.	Additives (50 mg each) with drug	Physical Observation	Observation at 45^{0}C after 6 month	Remarks
1.	Drug (Mesalamine)	White	No change	Accepted
2.	Drug + Eudragite-S 100	White	No change	Accepted
3.	Drug + Cellulose acetate Phthalate	White	No change	Accepted

3.3 Evaluation of Nanosphare

3.3.1 Particle size, surface morphology and zeta potential



(A)



(B) **(C)**

Figure 3- Scanning electron micrographs of (A) Nanosphare (B) Drug loaded nanosphare and (C) Polymer coated nanosphare

3.3.2 Drug entrapment efficiency

Drug entrapment efficiency of the formulations showed in the range of 90% to 96 %. The results have been shown in table.

Table 10 Drug Entrapment

Sr. no.	Batch no.	% Entrapment
1	F-1	94
2	F-2	96
3	F-3	92
4	F-4	93

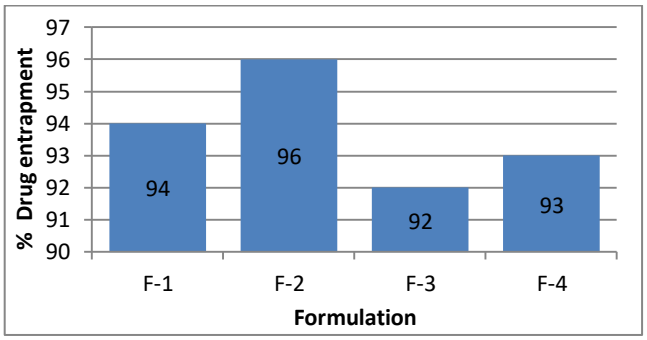


Figure 4 Drug Entrapment

3.3.4 *In-vitro* Drugrelease studies of Mesalamine nanosphare

Table 11 *In-vitro* Drugrelease studies of Nanosphare

Time (hr)	F-1	F-2	F-3	F-4
0	0.0	0.0	0.0	0.0
1	0.21	0.15	0.31	0.95
2	0.53	0.49	0.36	0.92
3	1.49	1.72	1.26	1.76
4	6.42	8.17	6.46	7.18
5	19.72	22.26	20.85	21.39
6	25.82	28.74	26.12	27.33
7	31.29	36.76	33.32	35.27
8	42.64	46.29	43.16	45.04
9	53.32	56.61	54.88	55.16
10	61.79	64.69	62.55	63.38
11	69.21	73.57	71.21	72.15
12	79.32	85.35	81.53	83.59
13	88.52	91.67	89.23	90.09
14	93.01	96.12	94.24	95.11
15	93.13	96.24	94.35	95.26

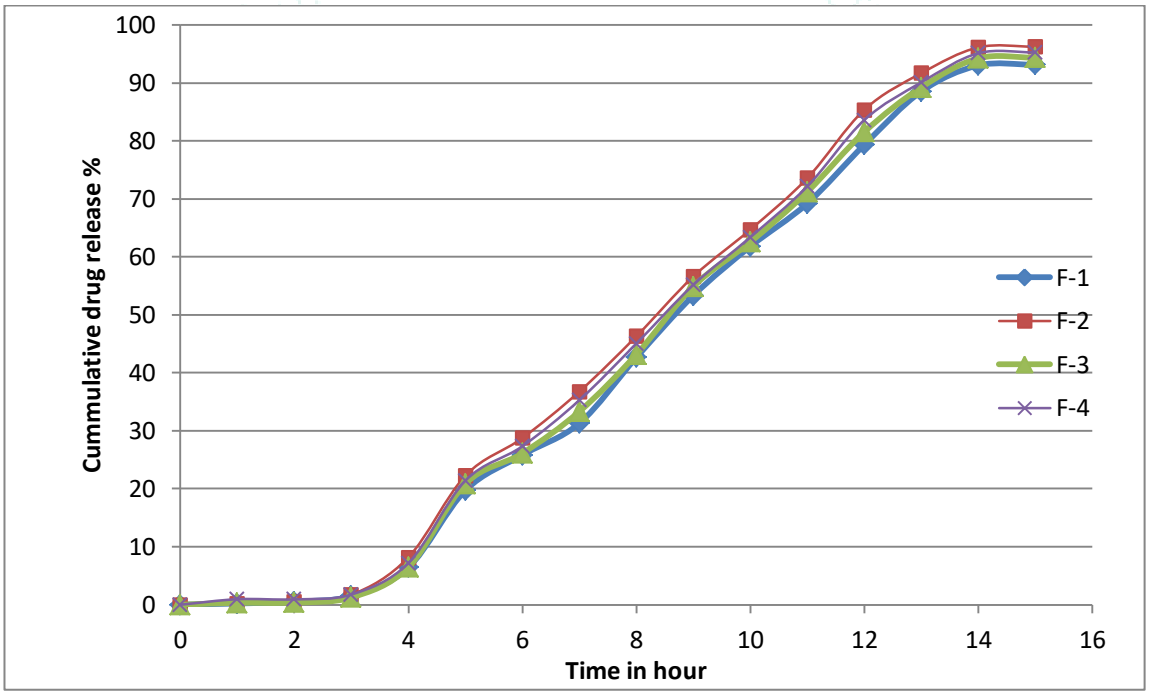


Figure 5 *In-vitro* Drugrelease studies of nanosphare

3.4 Evaluation of Nanosphare Tablet

3.4.1 Pre-compressed Parameter

Table 12 Pre Compressed Parameter

Formulation code	Angle of Repose(⁰)	Bulk density	Tap density	Hausner ratio	Carr's Index
F1	22⁰16 ± 0.5547	0.376 ± 0.016	0.415± 0.002	1.16± 0.001	15.55± 0.612
F2	20⁰54 ± 0.6548	0.364 ± 0.014	0.438± 0.006	1.15± 0.001	12.92± 0.554
F3	20⁰28 ± 0.4568	0.374 ± 0.017	0.446± 0.002	1.16± 0.002	14.23± 0.532
F4	21⁰22 ± 0.5449	0.352 ± 0.013	0.423± 0.003	1.17± 0.004	13.64± 0.368
F5	20⁰18 ± 0.5226	0.353 ± 0.011	0.424± 0.002	1.15± 0.004	14.78± 0.408
F6	21⁰09 ± 0.8547	0.358 ± 0.019	0.442± 0.004	1.16± 0.003	13.80± 0.309

3.4.2 Post Compressed Parameter

Table 13 Post Compressed Parameter				
Formulation code	**weight variation (mg) ± S.D**	**Hardness (Kg/cm²) ± S.D**	**Friability (%) ± S.D**	**Thickness (mm) ± S.D**
F1	610 ± 1.11	5.1 ± 0.218	0.32 ± 0.04	5.18±0.017
F2	608 ± 1.22	5.3 ± 0.225	0.32 ± 0.02	5.12±0.012
F3	609± 1.01	5.2 ± 0.363	0.33± 0.03	5.17±0.013
F4	611± 1.24	5.5 ± 0.106	0.31± 0.01	5.15±0.011
F5	607± 1.42	5.4 ± 0167	0.34± 0.05	5.11±0.014
F6	613± 1.51	5.3± 0.412	0.35± 0.06	5.14±0.012

*Values mentioned are average of 3 determinations

3.4.3 Drug content:

Table 14 Drug Content

Formulation	Drug Content (%)
F1	95.01
F2	96.32
F3	97.75
F4	92.58
F5	93.33
F6	94.47

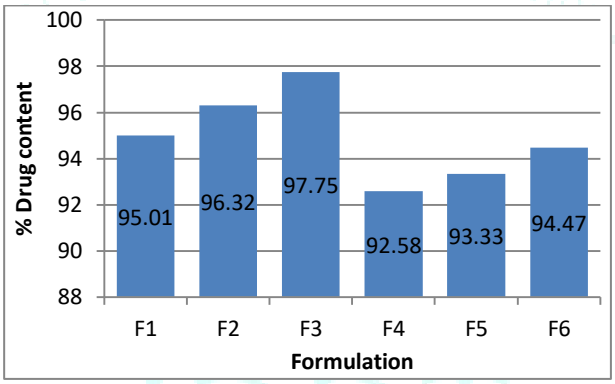


Figure 6 Drug content of different formulation

3.4.4 In-vitro drug release study of Mesalamine nanosphare tablet

Table 15 Cumulative Drug release (F-1 to F-6)

Time (hr)	F-1	F-2	F-3	F-4	F-5	F-6
0	0.0	0.0	0.0	0.0	0.0	0.0
1	5.31	6.11	6.32	4.19	5.22	4.95
2	9.36	10.42	11.63	5.19	6.31	8.92
3	14.26	15.74	16.74	8.04	9.16	13.76
4	18.46	20.13	22.56	12.49	14.34	17.18
5	25.85	27.25	29.81	17.72	19.81	24.39
6	31.12	33.74	35.88	22.35	23.09	30.33
7	38.32	39.76	41.34	26.49	28.04	36.27
8	45.16	46.29	48.73	32.57	34.33	43.64
9	50.88	52.61	53.37	39.16	40.49	48.16
10	55.55	57.69	59.88	45.63	46.45	54.38
11	61.21	63.57	65.43	51.08	52.24	59.15
12	67.53	69.35	70.55	56.31	57.58	64.59
13	73.23	74.67	76.76	62.34	64.23	71.09
14	82.05	83.53	82.34	69.73	71.54	81.32
15	85.09	87.24	88.45	76.15	79.01	84.28
16	93.91	94.85	96.57	87.89	89.12	92.95
17	93.92	94.89	96.58	87.92	89.14	92.97

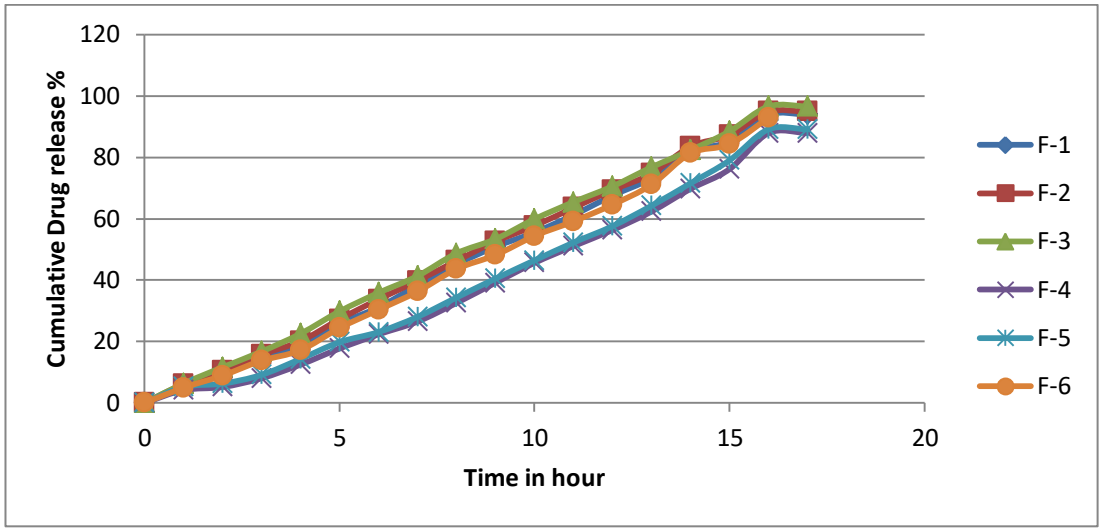


Figure 7 Cumulative Drug release % (F-1 to F-6)

3.4.5 Stability Study of optimized formulation

Table 16 Comparison of drug release after 6 month

Time (hr)	Inital	After 3 month
0	0.0	0.0
1	6.32	5.14
2	11.63	9.87
3	16.74	14.44
4	22.56	20.32
5	29.81	26.95
6	35.88	34.01
7	41.34	38.78
8	48.73	45.89
9	53.37	51.03
10	59.88	57.05
11	65.43	62.87
12	70.55	67.59
13	76.76	74.03
14	82.34	79.84
15	88.45	85.63
16	96.57	93.94
17	96.58	93.91

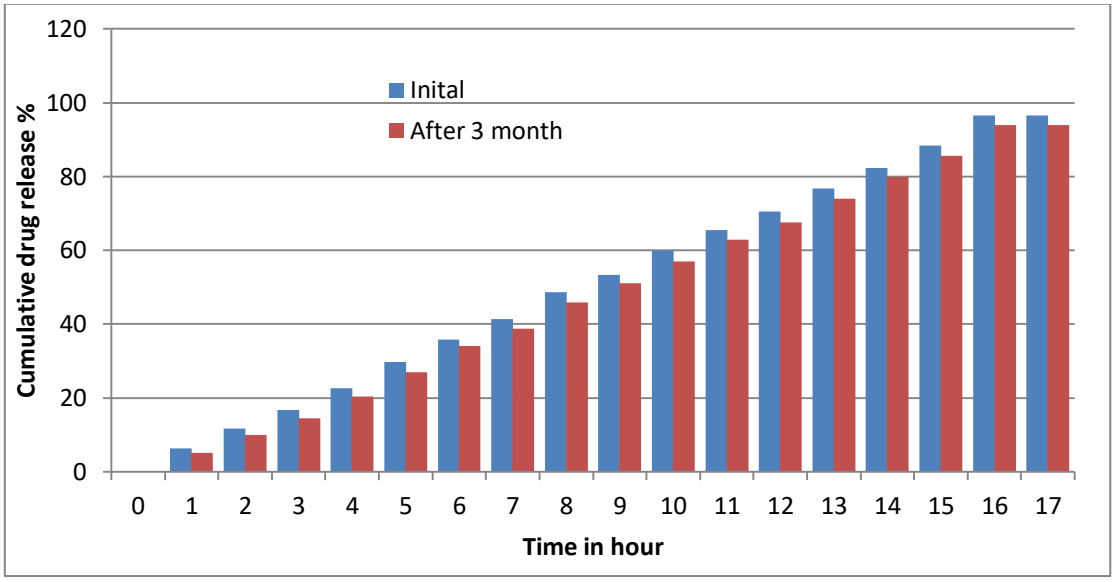


Figure 8 Comparative study ofdrug release after 6 month

4. CONCLUSION

On the basis of drug entrapment efficiency I concluded that method used for formulation of Nanosphare was optimized method. Formulation F-2 Showed 96% drug was entrapped which is best formulation among all other nanosphare formulation. Formulation F-3 showed least drug entrapment.*In-vitro* Drugrelease studies of Mesalamine nanosphare showed that Formulation F-2 release maximum drug (96.24%) after 15 hour.The FTIR spectra showed that drug and polymer used in formulation of Nanosphare tablet are compatible with each other.Nanosphare tablet formulation F-3 Showed maximum drug (97.75%) released and formulation F-4 showed 92.58% drug release.The *In-vitro* drug released study result showed that formulation F-3 96.58% drug was released after 17 hours which is highest drug release amongst all other tablet formulation.

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