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Research Article

Formulation Evaluation and Optimization of Mebendazole Colon Targeted Sustain Release Pellets by Extrusion Spheronization

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ABSTRACT

The aim of present investigation is to formulate evaluate and optimization of colon targeted pellets bearing mebendazole, benzimidazole derivative with broad spectrum of anthelminthic activity. It is highly effective against adult and larval stages of ascaris lumbricoids, hook worms and indicated for the treatment of nematode infestation. Pellets were prepared by extrusion spheronization process using microcrystalline cellulose as spheronizing aid, natural polysaccharide pectin as binders in three different percentages i.e 5%, 10% and 15% and glycerine as plasticizer. Further study was carried out to select the natural polysaccharide for formulation of colon targeted pellets i.e. Pectine, Xanthan gum and Guar gum. The formulation were prepared with optimized constant process parameters i.e. Percentage LOD 10%, Spheronization time 3 minutes and Speed of spheronization 700-1200 rpm. Prepared A1 – A9 batches were then evaluated by their micromeritic properties like tapped density, carr's index, hausner, S ratio, angle of repose and characterized by microscopic study, % yield, hardness, friability, % assay and dissolution study was carried out and compared with marketed formulation by statistical analysis similarity factor (f_2). The batch A5 is having 10% pectin, 18% MCC and 20% mebendazole shows (22.20±2.05) % carr's index, (1.22±0.04) hausner's ratio, (26.65±1.15) angle of repose, (88.2±2.36) % yield, (3.96±0.46) hardness, (0.23±0.03) % friability (88.47±3.26) % assay and (99.81±3.80) % drug release after 10 hours. Pellets equivalent to 300mg of mebendazole were then filled in capsules and capsules coated with 12.5% w/v Eudragit S 100 using optimized 4- 5 ml/min spray rate, 15 rpm pan speed and 40±5°C coating inlet temperature and then optimized for % weight gain in four different trials. W2 batch having 10% weight gain were then evaluated by % cumulative drug release, disintegration test in 0.1 N HCl shows (99.73±3.34) % CDR, intact after 12 hours. The pellets of batch A5 and the enteric coated capsule with 10 % weight gain were packed in aluminum pouch and charged for accelerated stability studies at (40°C±2°C) and (75%±5%) RH for 1 month in a stability chamber shows no change in the dissolution profile at (40°C±2°C) and (75%±5%) RH storage condition.

Keywords: Mebendazole, Colon Targeted delivery, Sustain Release, Extrusion Spheronization

INTRODUCTION

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the gastrointestinal tract (GIT) depends upon the physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs

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in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs into the colon rather than upper GIT prefers number of advantages. A traditional oral sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in the colon or throughout the gastrointestinal tract.[1] Mebendazole comes under the category Anhtelminthic. Mebendazole is benzimidazole derivative with broad spectrum of anthelminthic activity. It is highly effective against adult and larval stages of ascaris lumbricoids, enterobious vermicularis, and hookworms. Recent in vitro studies have reported that mebendazole is more effective than metronidazole in killing giardia lamblia. The dose of mebendazole is 100 mg twice a day (200mg), having a bioavailability less than 20%. Its t_{max} is 0.5 to 7 hrs and C_{max} is 0.03mcg/ml. Its half life is 2.5 to 5 hrs. It is short half life which favors to development of sustained release.[2] Natural polysaccharides like pectine, guar gum, xanthan gum are now extensively used for the development of solid dosage forms for delivery of drug to the colon. The rational for the development of a polysaccharide based delivery system for colon in the presence of large amounts of polysaccharides in the human colon. The colon is inhibited by a large number and variety of bacteria which secrete many enzymes e.g. ß-D glucosidase, ß-Dgalactocidase, amylase, pectinase, dextranase, etc.[3]

Report suggests that drug carrier system larger than 200 µm possess very low gastric transit time due to physiological condition of the bowel in colitis and for this reason and considering the selective uptake of micron or submicron particles by cancerous and inflamed cells/tissues. Multiparticulate approach based on pellets, granules, microsphere or nanoparticle type formulation is expected better pharmacological effect in the colon. Pellets can be formulated with size near to 1mm. Since the drug has shorter half life 2.5 to 5.0 hours, it is primarily metabolized hepatically into its inactive form and having 20% bioavailability when given orally. So, By formulating the colon targeting SR pellets of Mebendazole which contains biodegradable polysaccharides as sustain release binding agent prevent first pass metabolism, provide increase residence time resulting in prolonged drug delivery in colon and improve patient compliance by reducing dosing frequency.

MATERIALS AND METHODS

Table 1: Materials used in present investigation :

Mebendazole	Welable Healthcare, Mehsana
Pectin	S.D. Fine Chemicals Ltd
Xanthan gum	S.D. Fine Chemicals Ltd
Guar gum	S.D. Fine Chemicals Ltd
Eudragit S 100	Corel Pharmaceuticals, Ahmedabad, India
Glycerine	S.D. Fine Chemicals Ltd
MCC	S.D. Fine Chemicals Ltd
TEC	S.D. Fine Chemicals Ltd

Microcrystalline Cellulose as Spheronization aid:

In relation to the above-mentioned requirements of the wetted mass, microcrystalline cellulose (MCC) is incorporated

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in most formulations processed via extrusion–spheronisation, since it provides the proper rheological properties to the wetted mass for successful extrusion and spheronisation. MCC is the golden standard as extrusion–spheronisation aid based on its good binding properties that provide cohesiveness to a wetted mass containing MCC. Furthermore, it is able to absorb and retain a large quantity of water due to its large surface area and high internal porosity, thus facilitating extrusion, improving wetted mass plasticity and enhancing spheronisation. Moreover, by controlling the movement of water through the plastic mass, it prevents phase separation during extrusion or spheronisation. Due to these properties MCC-based pellets produced via extrusion–spheronization have a good sphericity, low friability, high density and smooth surface properties. Furthermore, from a processing viewpoint, relatively wide ranges of water content and processing parameters can be employed to provide pellets with acceptable quality, indicating the robustness of the formulations.[4,5]

Mechanism of Spheronization aid:

MCC is described as a 'molecular sponge'. The MCC particles are able to retain water in a manner similar to a sponge. During extrusion these sponges are compressed, and water that is squeezed from the internal structures acts as a lubricant. After extrusion, the volume of the sponges expands and they appear dry and brittle, which facilitates the breaking of the extrudates during the initial phase of spheronisation. During the spheronisation phase, the sponges are densified due to collisions between particles and the spheronizer plate and wall, and water facilitates spheronisation of pellets.[6,7]

Characteristics of MCC:

- Water insolubility
- Large water absorption and retention capacity
- Binding properties
- Sufficiently large surface area for interaction with water and other ingredients in the powder mixture.

EUDRAGIT S 100 offers valuable advantages for enteric coatings:[8]

- PH-dependent drug release
- Protection of actives sensitive to gastric fluid
- Protection of gastric mucosa from aggressive actives
- Increase in drug effectiveness
- Good storage stability
- GI and colon targeting

METHODOLOGY

Preformulation study:[9]

It is the first step in rational development of dosage forms of drug substance. Preformulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass-produced.

a)Organoleptic properties:[9]

The drug sample was evaluated for its colour, taste and odour.

b) Melting point determination:[10]

Melting point of the drug sample was determined by capillary method by using melting point apparatus.

c) Solubility analysis:

Solubility analysis was carried out for the selection of suitable solvent for further processing to formulation. It was carried out by making saturated solution of drug in various solvents separately, then filtered it and analyse by UV spectrophotometric technique.

d) Determination of λ_{max} :

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Determination of λmax of drug (mebendazole) is carried out by screening method. In this method making a suitable diluted solution of mebendazole in suitable solvent and scanned for the maximum absorbance in the range of 200 nm – 400 nm on Shimadzu 1700 UV/Vis double beam spectrophotometer.

e) Determination of Calibration curve:

1) Standard calibration curve of Mebendazole in 0.1N HCl + 1% SLS

Calibration curve of drug was taken in 0.1N HCl + 1% SLS. Absorbance was measured at λ_{max} 291 nm using UV visible double beam spectrophotometer of solution.

2) Standard calibration curve of Mebendazole in phosphate buffer pH 7.4

Calibration curve of drug was taken in phosphate buffer pH 7.4. Absorbance was measured at λ_{max} 291 nm using UV visible double beam spectrophotometer of solution.

f) Drug excipient compatibility Study:

1) Fourier-transform infrared spectroscopic study:

Infrared spectra of pure drug, polymer, as well as for combination of drug-polymer were taken by KBr pellet technique and were recorded in the range of 4000 – 400 cm^{-1} by using FT-IR Spectrophotometer.

2) Differential Scanning Calorimetric (DSC) study:

All the samples were tasted on DSC-60 Shimadzu by controlled heating at the rate $20^{o}C$/min in air environment in range of $50^{o}C$ to 300^{o} c.

Preparation of pellets:[11]

The wet extrusion process can be batch or continuous operation and consists of the following steps:

1. Mixing

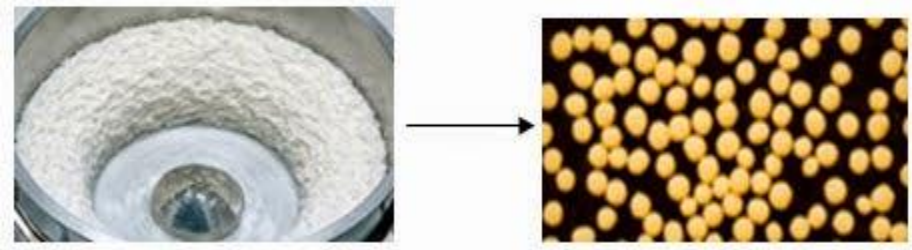
First of all weigh accurately as per quantity of drug, MCC, DCP and mix well in motor pistal. Then add binder solution as per required and make a dump mass. Here different binders were used like pectin, xanthan gum and guar gum. These all binders are natural polysaccharides and natural polysaccharides are completely digested by colonic enzymes.

2. Extrusion

Then this mass is put in extruder for getting extrudes as shown in **figure1.**

3. Spheronization

The wet extrudates are placed in an oven for optimum % LOD (Loss on Drying). If there was higher moisture then extrudes stick with each other and if it was less then there were chances of fine particles. After this stage extrudes were placed in spheronizer for getting sphere pellets as shown in **figure 2.**



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4. Drying

These wet spheres are then transferred to a FBD dryer for drying process.

Preliminary trial batches for optimization of process variables :

Fixed parameters:

· Extruder screen size: 0.87mm
· Extruder speed: 60rpm
· Final pellets drying temperature: 50^{o}C
· Final pellets drying time: 30minutes

Variable parameters:

· %LOD (Loss on drying) of extrudes: 10%, 15%, 20%, 25%
· Spheronization time: 120sec, 180sec, 300sec, 420sec.
· Spheronization speed: 700rpm, 1000rpm, 1300rpm

Table 2 : Preliminary trial batches :

Batches	Pectin	MCC	DCP	Glycerin
P1	5%	18%	57%	2ml
P2	10%	18%	52%	2ml
P3	15%	18%	47%	2ml

1) Optimization of % LOD
2) Optimization of spheronization speed.
3) Optimization of spheronization time.

By using the trial and error method the effect of %LOD, spheronization time and spheronization speed on % yield in desired size range, sphere size, and sphere shape were evaluated. By using the 20% of % LOD, spheronization time 180 seconds, and spheronization speed 1000rpm results were obtained for the % yield, sphere size, and sphere shape. Sphere size and shape was depended on the spheronization speed and % LOD in the extrudes to be spheronized, whereas the % yield was significantly affected by spheronization time.

Composition of pellet formulation:

The study continues further for selection and optimization of polymer for colon targeted pellets. The selection of polymer initial short listed based on literature survey and availability to three different natural polymer and their three different percentages. The polymers used were pectine, xanthan gum and guar gum in three different percentages i.e. 5 %, 10 % and 15%w/w. These polymers are natural polysaccharides which are completely digested by colonic enzymes e.g. ß-D glucosidase, ß-D-galactocidase, amylase, pectinase, dextranase, etc and also they are cheap in cost.

In table there was fixed the quantity of MCC, Drug and glycerin. Here glycerin was used for plasticity of extrudes. The typical composition of formulation showed in table 6.5. Prepared pellets were evaluated for micromeritic properties and flow characteristics. (Bulk density, tapped density, Carr's index, and angle of repose).

Table 3 : Composition of pellets formulations A1-A9 :

Batches	Xanthan gum (w/w)	Pectin (w/w)	Guar gum (w/w)	MCC (w/w)	DCP (w/w)	Drug (w/w)	Glycerine (ml)
A1	5%	-	-	18%	57%	20%	2ml
A2	-	5%	-	18%	52%	20%	2ml

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A3	-	-	5%	18%	47%	20%	2ml
A4	10%	-	-	18%	57%	20%	2ml
A5	-	10%	-	18%	52%	20%	2ml
A6	-	-	10%	18%	47%	20%	2ml
A7	15%	-	-	18%	57%	20%	2ml
A8	-	15%	-	18%	52%	20%	2ml
A9	-	-	15%	18%	47%	20%	2ml

EVALUATION OF PELLETS

1) Tapped density = m/v_t
m = Mass of pellets
v_t = Tapped volume

2) **Carr's index(%) =** [ρt -ρb/ρt] ×100
ρb = Bulk density
ρt = Tapped density

3) Hausner's ratio = ρt/ρb
ρt = Tapped density
ρb = Bulk density

4) Angle of repose:
The angle of repose for the pellets of each formulation was determined by the funnel method. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation: $\tan \theta = H / R$ Therefore; $\theta = \tan^{-1} (H / R)$.[12,13]

5) SEM analysis:
Samples of pellets of A5 batches were dusted on onto silica gel applied sample holder. The samples were imaged using 15 kV electron beam.

Characterization of batches for process variables:
1)Microscopy study of pellets:
Photomicrographs of the pellets obtained from various batches were taken using a fluorescence microscope (Leica inverted fluorescence microscope).

2) Percentage yield:
It was calculated by following formula.[14]

$$\% \text{ Yield} = \frac{\text{Weight of yield in desired size range}}{\text{weight of practically obtained total yield}} \times 100$$

3) Hardness of pellets:
Hardness of pellets was measured by using digital pharmatest hardness tester.[14]

4) Friability test:
Friability test for pellets was carried out using Roche friabilater

5)Assay:
Assay of the drug was performed by UV spectroscopy method. The absorption of the solution has measured at 291 nm by UV spectroscopy method.[15]

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Dissolution profile of batch A1-A9 in phosphate buffer pH-7.4:

The drug release study was carried out using auto sampler dissolution test apparatus USP type 1 basket (TDT-08L, Electrolab, Mumbai, India.) at 37°C ± 0.5°C and at 100 rpm using 900 ml of phosphate buffer of pH 7.4 as dissolution medium as per USP XXVI. Percentage drug dissolved at different time intervals was calculated using the Lambert-Beer's equation from the calibration curve.[16]

Comparison of dissolution profile by statistical analysis similarity factor (f_2):

The dissolution profiles of products were compared using f_2. The similarity factor is calculated by following formula, [10]

$$f_2 = 50 \mathrm{X} \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} \mathrm{X}\, 100\right\}$$

Where, n is the number of dissolution time points

R_t - The reference profile at the time point t

T_t - The test profile at the same point.

Eudragit coating on capsules of optimized batch :

Eudragit S 100 has 12.5% availability in organic solution and dissolve pH >7.

Table 4 : Optimised batch for coating process :

Materials	Quantity
Drug	20%
MCC	18%
DCP	57%
Pectin	10%
Guar gum	2ml

Table 5 : Composition of coating solution :

Ingredients	Quantity
Eudragit S 100	12.5 %
Talc	2 %
Tri ethyl citrate (TEC)	2%
Methanol : Acetone (5:5)	q.s.

Coating process:

The hard gelatin capsules of size 0 were filled with pellets of mebendazole of the optimized batch A5. Pellets equivalent to 300mg of mebendazole were filled in each capsule. The enteric coated capsules were prepared by using conventional coating pan. Coating solution was prepared by dissolving coating polymer in to the Methanol and Acetone mixture (1:1) and uniform dispersion of coating solution was spray on the capsule bed under the following condition until desired coating thickness was obtained.

About 10 capsules of mebendazole sustained release matrix pellets were taken and allow to coating in pan coater at 15 rpm and 40°C temperature. Coating was carried out with spraying method and dried with same.[16]

Table 6: Process parameters for coating :

Spray rate	4-5 ml/min
Pan speed	15 rpm
Hot air inlet temperature	40 ± 5°C

The coated capsules were dried for 10-15 min. in coating pan. The amount of coating was done up to 5 to 20% per capsule. The % weight gain was then optimized considering the in vitro dissolution test.

Optimization of process parameters:

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In process optimization study, optimization of % weight gain of capsules, inlet air temperature and pan speed were carried out.

1) Effect of different weight gain:
To know the effect of different weight gain; four trials were taken with four different % weight gains and % weight gains of the batches were 5 %, 10% , 15% and 20%.

2) Effect of different Inlet Temperature.[17]
To know the effect of different inlet air temperature three batches were taken with three different temperatures 30º, 40º and 50° C and coating process continue till 10 % weight gain achieved in each batch.[15]

3) Effect of different speed of rotating pan:
Hence coating was performed at different rotating speed of pan 5, 10, and 15 rpm at constant inlet air temperature (40° C) and coating process continued till 10 % weight gain was achieved in each batch.

Evaluation of enteric coated capsules:
After and during enteric coating procedure capsules were evaluated for % weight gain, disintegration test.

1) Weight gain:
It was calculated using following equation.
$\% Wg_a = [(Wt_a - Wt_b) Wt_b] \times 100$

Where, Wt_b and Wt are the total batch weights before and after coating, respectively.

2)Disintegration test:
Disintegration testing of coated dosage forms was carried out in the six tablet basket rack USP disintegration apparatus maintained at 37°C ± 2°C using dissolution medium 0.1 N HCl for first 2 hours, phosphate buffer pH 6.4 after 2 hours and phosphate buffer pH 7.4 after 3 hours.

Evaluation of optimized enteric coated batch:
It was carried out using pan coater at speed 15 RPM, inlet air temperatures kept at 40°C. Eudragit dispersion was applied until 10 % weight gain achieved.

Accelerated stability testing of the optimized Batch:
The pellets of batch A5 and the enteric coated capsule with 10 % weight gain were packed in aluminum pouch and charged for accelerated stability studies at 40°C and 75% RH for 1 month in a stability chamber.

RESULT AND DISCUSSION

Preformulation study:

a) Organoleptic properties:

Table 7 - Results of organoleptic properties	
Properties	**Results**
Color	Off white to slightly yellow
Odor	Amorphus
Taste	Unpleasant

b) Determination of melting point:
Table 8 : Result of melting point :

Reported Melting Point	**Observed Melting Point**

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288°C	286°C - 290°C

c) Solubility study :

Table 9 : Result of solubility study :

Solvents		Terms
Water		Less than 0.05 %
0.1N HCl		Less than 0.05 %
Formic Acid		Soluble
Phosphate buffer	pH 6.8	Soluble
	pH 7.4	Soluble
Chloroform		Insoluble
DCM(Dichloromethane)		Soluble

d) Determination of caliberation curve:

Table 10.1 : Calibration curve of mebendazole in 0.1 N HCL+ 1% SLS at 291 nm

Sr. No	Concentration (µg/ml)	Absorbance			Average absorbance
1	5	0.170	0.165	0.175	0.170±0.005
2	10	0.339	0.345	0.333	0.339±0.006
3	15	0.467	0.470	0.464	0.467±0.003
4	20	0.660	0.654	0.666	0.660±0.006
5	25	0.784	0.790	0.778	0.784±0.006
6	30	0.957	0.963	0.951	0.957±0.006

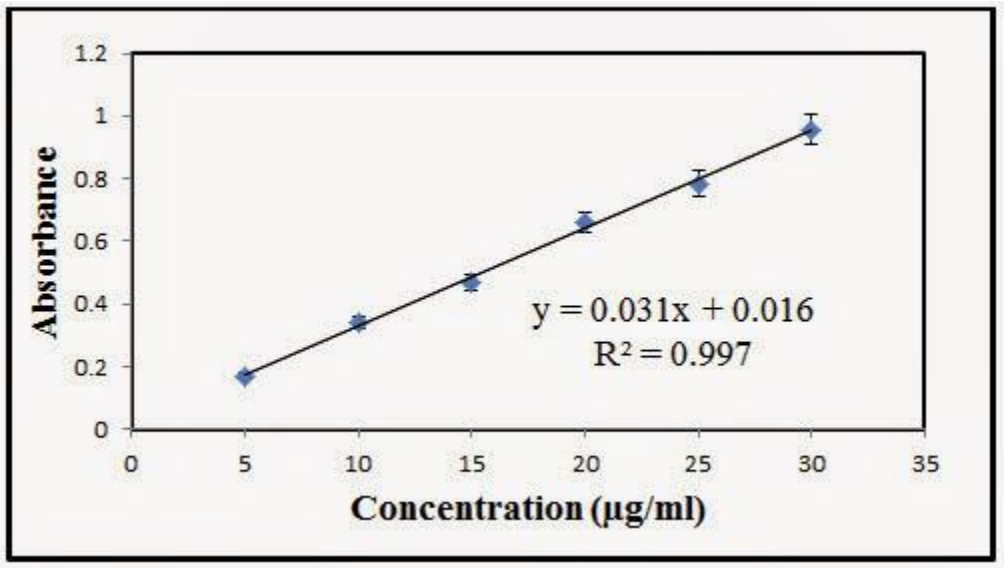

Figure 3.1: Calibration curve of mebendazole in 0.1 N HCL + 1% SLS

Table 10.2: Calibration curve of mebendazole in phosphate buffer pH 7.4 at 291 nm

Sr. No	Concentration (µg/ml)	Absorbance	Average absorbance

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1	5	0.198	0.199	0.198	0.198±0.0005
2	7.5	0.274	0.268	0.280	0.274±0.006
3	10	0.563	0.558	0.568	0.563±0.005
4	15	0.836	0.845	0.827	0.836±0..009
5	20	0.982	0.968	0.996	0.982±0.014

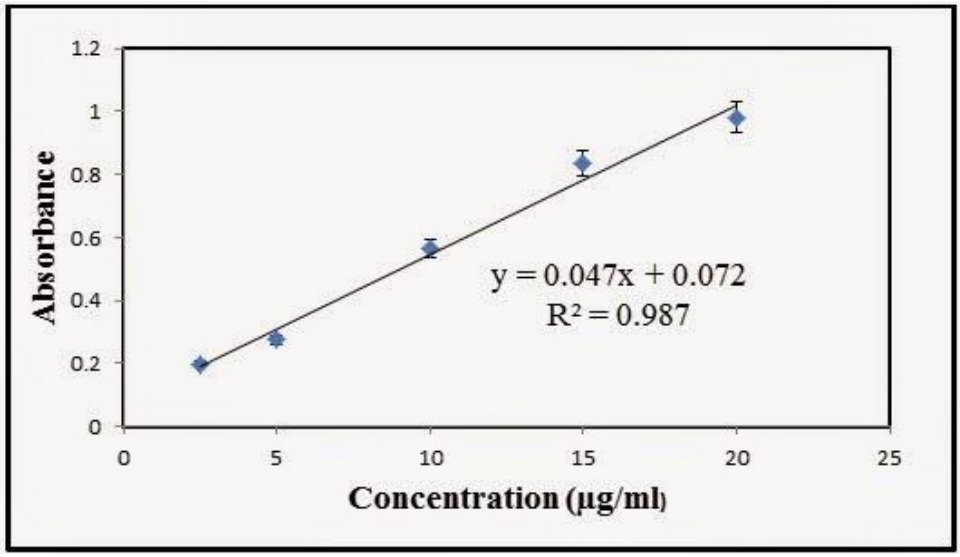

Figure 3.2: Calibration curve of mebendazole in phosphate buffer pH 7.4

e) Drug Excipient Compatibility study:

Fourier-transform infrared spectroscopic study :

In the present study, it has been observed that there is no chemical interaction between mebendazole and excipients used. Drug has given peaks due to benzimidazole ring. From the figure 4.2 it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and excipients, which showed that there were no physical interactions or some bond formation between drug and excipients.

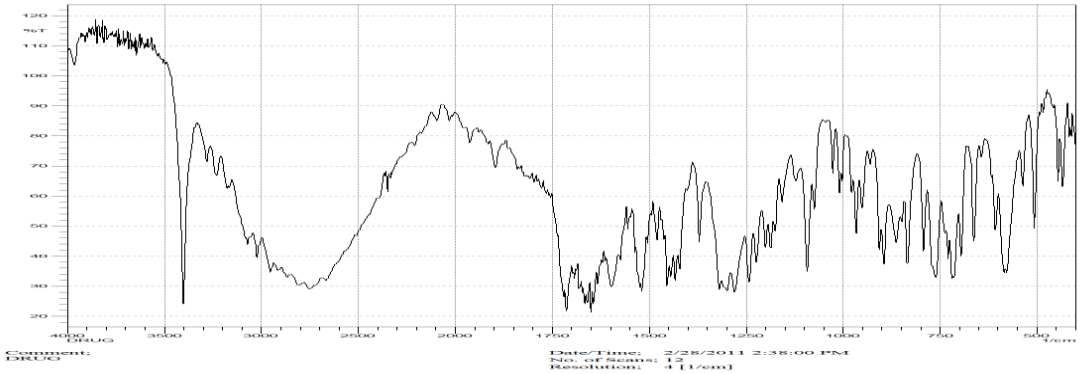

Figure 4.1: FTIR study of Drug

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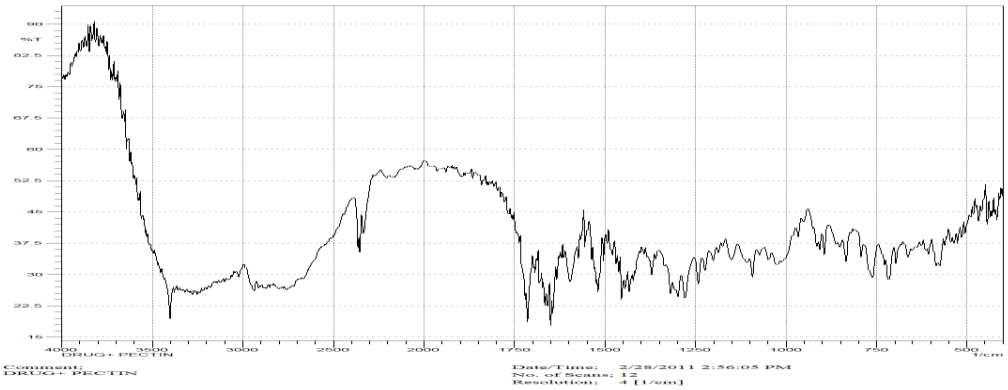

Figure 4.2: FTIR study of Drug + pectin.

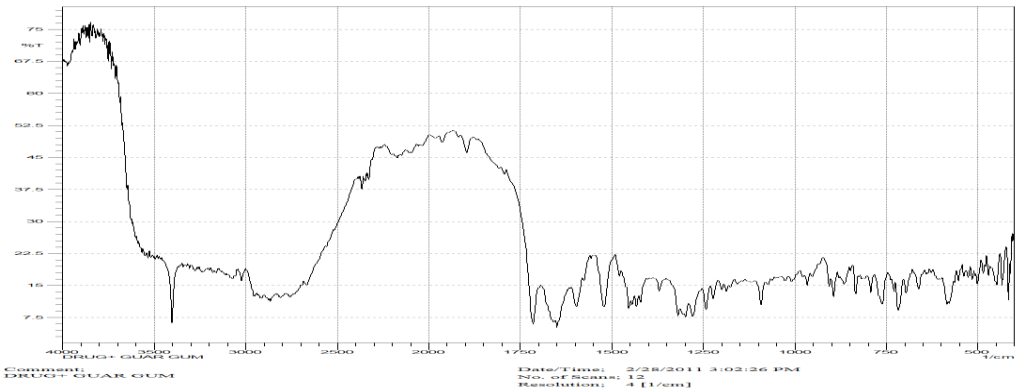

Figure 4.3 : FTIR Study of Drug + xanthan gum

The chemical interaction between the drug and the binder often leads to identifiable changes in the infrared (IR) profile of mixture.

The selection of excipients and its compatibility with the drug can be determined by the preformulation studies. The FTIR spectra of drug alone and in combination with different excipients were showed the compatibility between drug and selected excipients. Hence further design trials were conducted using these excipients

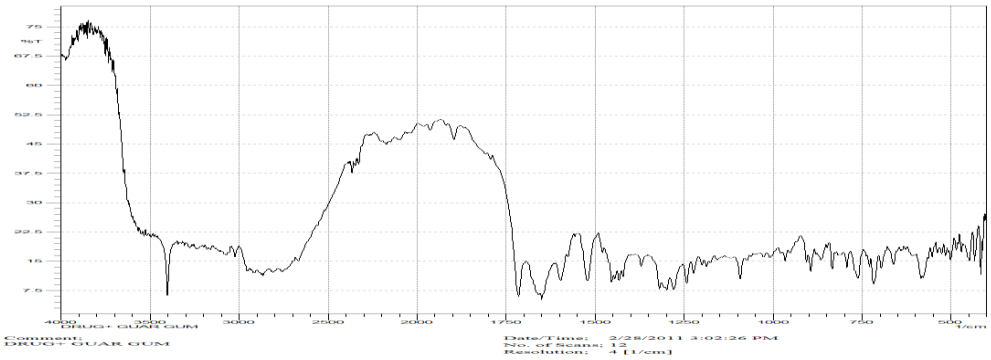

Figure 4.4 : FTIR Study of Drug + Guar gum

2) Differential Scanning Calorimetric (DSC) study:

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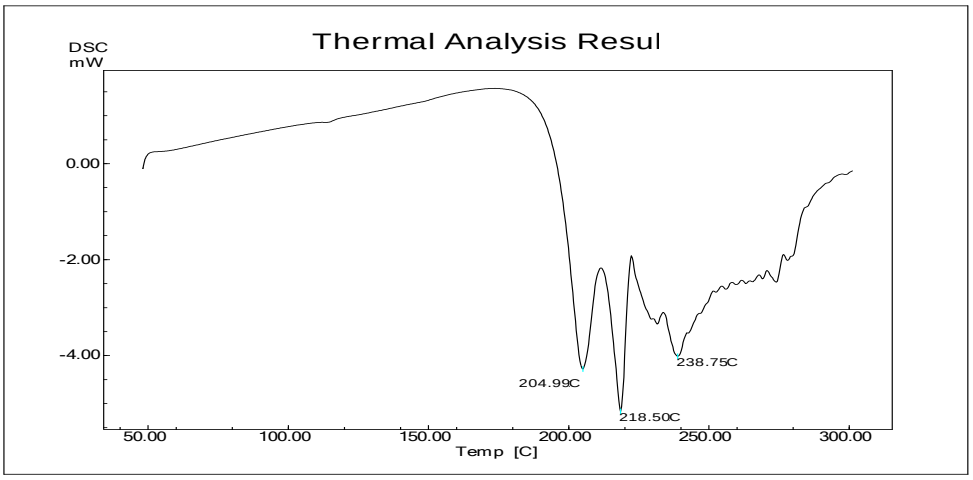

Figure 5.1 : Differential Scanning Calorimetric (DSC) Thermograph mebendazole drug.

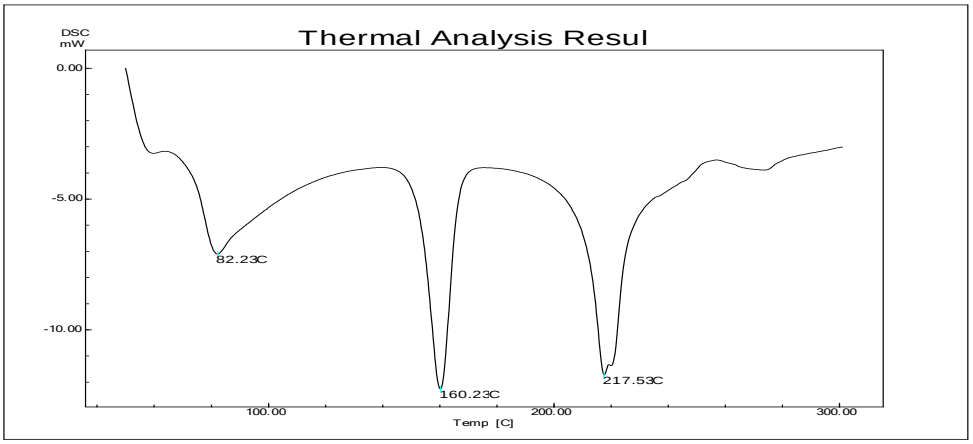

Figure 5.2 : Differential Scanning Calorimetric (DSC) Thermographs drug + pectin.

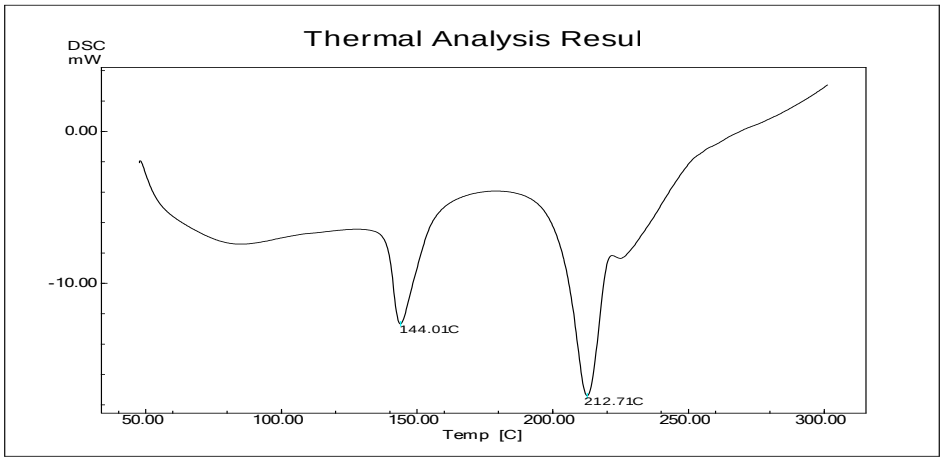

Figure 5.3 : Differential Scanning Calorimetric (DSC) Thermographs of formulation.

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Figure: 5.1, 5.2, 5.3 shows DSC results of mixture and formulation. From the thermograph, 5.1 shows the mixture having peaks at 160.01°C and 217.53°C, 5.2 shows first peak at 144°C and the second peak are achieved at 212°C. Both the peaks were similar to mixture peaks.

Evaluation of pellets:

Table 11 : Results of micromeritic properties of pellets :

Batch No.	Car's index (%)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Angle of repose
A1	36.67±1.60	0.692±0.003	1.05±0.03	1.52±0.03	24.56±2.06
A2	30.00±2.54	0.666±0.005	0.952±0.003	1.43±0.05	26.36±1.22
A3	26.66±1.65	0.666±0.008	0.909±0.006	1.36±0.03	32.76±2.36
A4	18.52±1.02	0.737±0.002	0.952±0.004	1.29±0.02	28.54±3.14
A5	22.20±2.05	0.741±0.004	0.909±0.003	1.22±0.04	26.65±1.15
A6	19.08±1.97	0.714±0.009	0.892±0.005	1.25±0.03	29.46±2.18
A7	08.33±1.25	0.833±0.006	0.909±0.004	1.09±0.05	24.78±1.62
A8	11.49±1.69	0.769±0.007	0.869±0.007	1.13±0.04	25.94±1.04
A9	11.08±1.46	0.740±0.006	0.833±0.006	1.12±0.07	30.76±3.28

6) Scanning electron microscopy:

Figure 6.1 : SEM of pellets with 37 times magnification

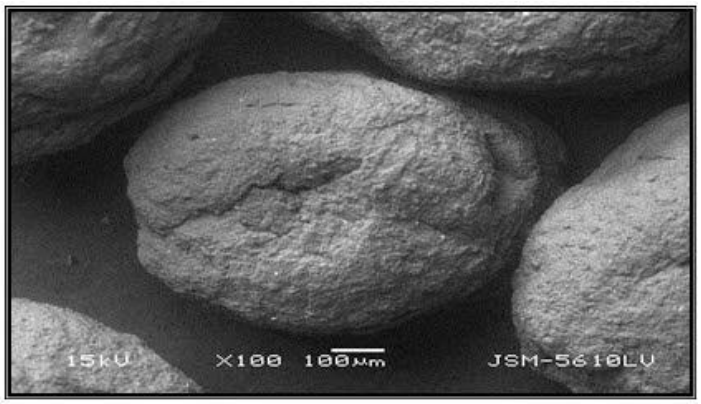

Figure 6.2: SEM of pellets with 100 times magnification

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Figure: Results of scanning electron microscopy for shape and morphology Of pellets 6.1 SEM of pellets with 37 times magnification

6.2 SEM of pellets with 37 times magnification.

Characterization of pellets:

Microscopic study of pellets

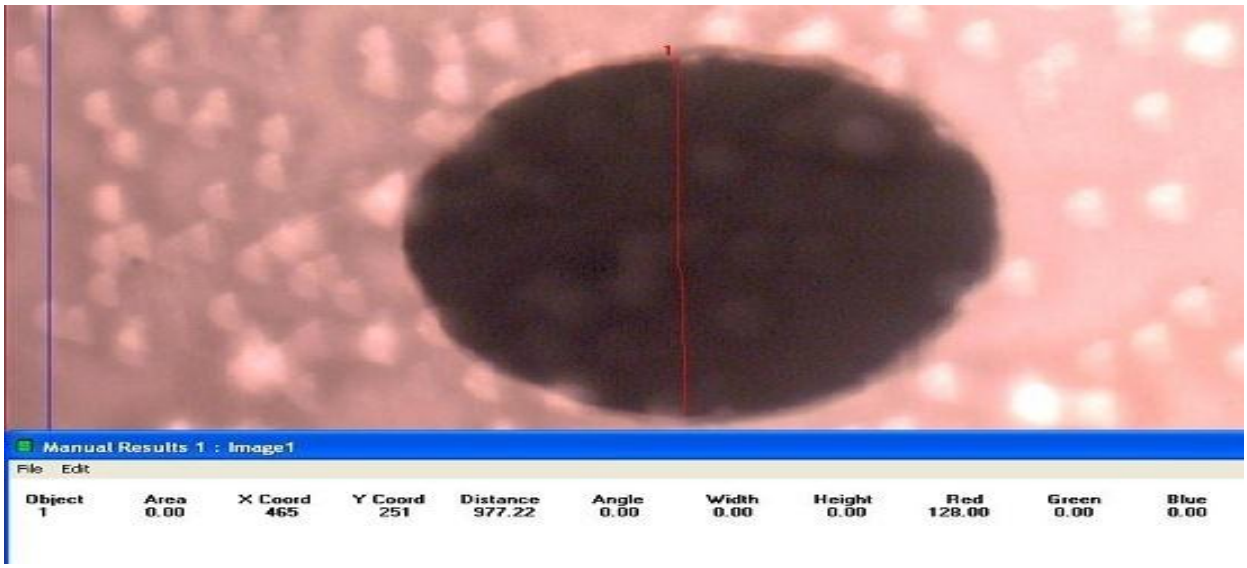

Figure 7 : Microscopic study of pellet in Leica Fluorescence microscope

Table 12 : Results of Characterization of pellets:

Batch	%yield	Hardness	%Friability	% Assay
A1	72 ±3.5	1.39±0.03	1.67±0.06	83.32±4.5
A2	81 ±2.8	2.56 ±0.06	1.07±0.13	82.32± 3.37
A3	83 ±5.4	1.78 ±0.04	1.33±0.24	73.36± 2.26
A4	75 ±3.6	3.78 ±1.02	0.29± 0.05	85.60± 5.48
A5	88±2.36	3.96 ±0.46	0.23±0.03	88.47± 3.26
A6	78 ±4.9	2.89 ±0.27	0.27± 0.07	81.88± 2.72
A7	79 ±5.6	3.98 ±0.34	0.58±0.04	69.90± 4.25
A8	87 ±2.8	4.55 ±0.65	0.42± 0.02	79.95± 3.15
A9	78 ±3.2	3.04 ±0.87	0.56± 0.08	81.65± 2.82

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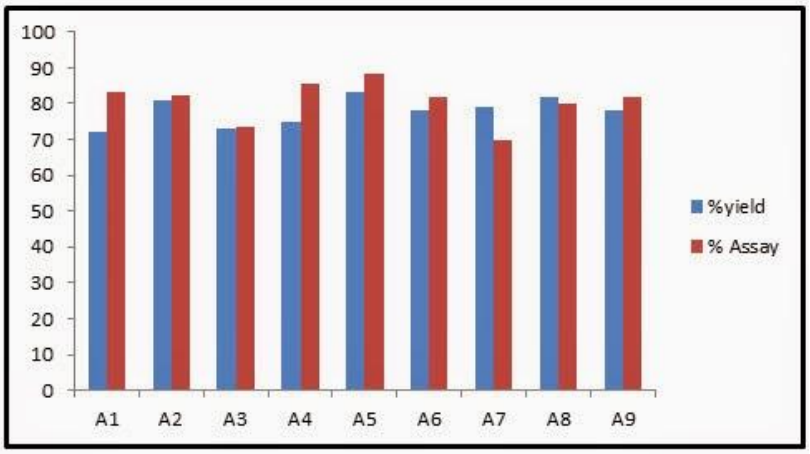

Figure 8 : Graphical % yield and % assay

Dissolution profile of batch A1-A9 in phosphate buffer pH- 7.4:

Table 13.1 : % Drug release of batch A1-A3.

Time (hrs)	A1	A2	A3	Marketed Formulation
0	0.00	0.00	0.00	00
1	46.50±4.5	41.54±3.2	38.40±3.4	29.36 ±3.06
2	58.45 ±2.67	48.53±4.33	46.67 ±2.37	48.78 ±4.04
3	69.98 ±3.9	56.12 ±2.16	56.85 ±4.65	58.96 ±3.46
4	73.56 ±3.5	60.79 ±3.49	65.04 ±3.02	67.87 ±3.27
5	81.94 ±3.97	63.62 ±2.42	72.28 ±2.18	72.23±2.20
6	90.83 ±2.8	70.17 ±4.03	78.25 ±2.25	79.56 ±4.56
7	96.31 ±4.32	74.41 ±3.21	82.81 ±4.41	83.78 ±3.70
8	85.96 ±2.96	79.59 ±3.05	86.20 ±4.05	89.65 ±4.35
9	89.24 ±3.24	84.60 ±2.40	89.76 ±3.65	96.78 ±2.70
10	92.82 ±2.8	89.11±4.01	94.02 ±5.01	102.08 ±4.06
f_2 value	68.83±3.6	62.43±4.23	71.68±2.32	

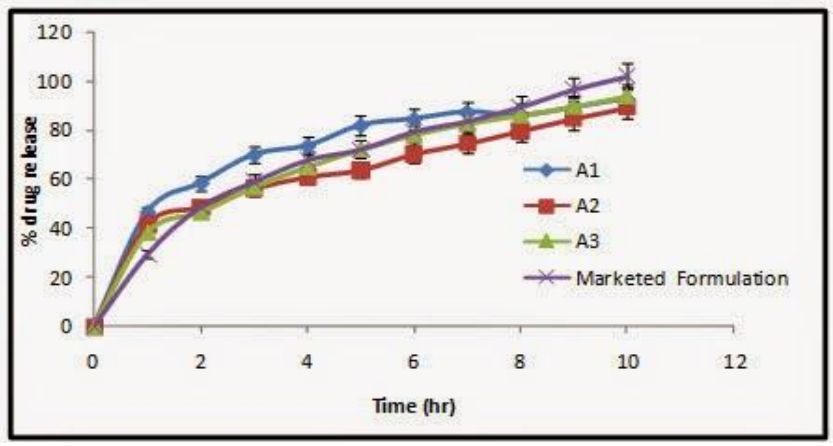

Figure 9.1 : % Drug release of batch A1-A3

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Table 13.2: % Drug release of batch A4-A6

Time(hrs)	A4	A5	A6	Marketed Formulation
0	0.00	0.00	0.00	00
1	38.97±3.07	36.52±2.12	34.80±2.65	29.36±3.06
2	48.18 ±4.15	47.20±2.05	45.95±1.79	48.78±4.04
3	56.93 ±2.03	54.71±3.7	54.21±4.20	58.96 ±3.46
4	63.39 ±3.59	60.65±4.25	60.78±3.40	67.87±3.27
5	69.52±4.12	66.10±3.05	66.72±2.70	72.23±2.20
6	72.63 ±2.33	71.82±3.42	71.39±2.65	79.56±4.56
7	77.41 ±5.41	78.65±3.25	76.03±4.67	83.78±3.70
8	83.95 ±3.55	84.00±2.05	80.18±3.10	89.65±4.35
9	88.65 ±4.05	92.60±4.45	84.37±2.35	96.78±2.70
10	92.55 ±2.50	99.81±3.80	89.04±4.68	102.08 ±4.06
f_2 value	67.56±3.5	78.56±2.06	64.43±3.26	

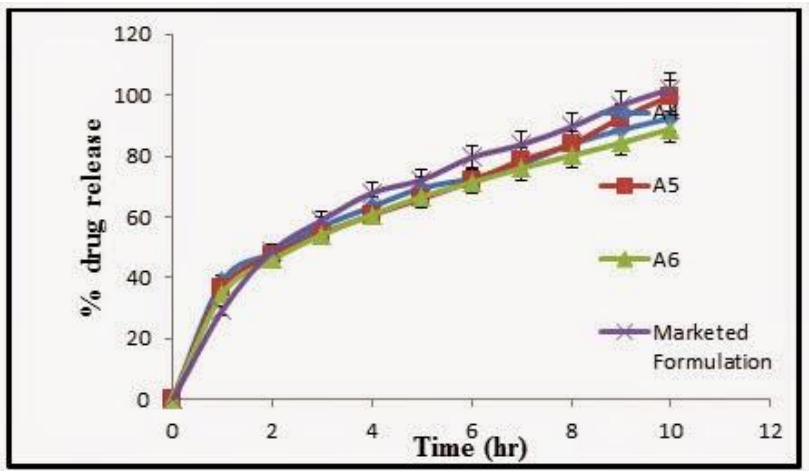

Figure 9.2 : % Drug release of batch A4-A6

Table 13.3: % Drug release of batch A7-A9.

Time(hrs)	A7	A8	A9	Marketed Formulation
0	0.00	0.00	0.00	00
1	31.18±3.38	30.19±2.37	29.21±4.01	29.36±3.06
2	37.94±2.54	36.06±3.05	35.34 ±2.14	48.78±4.04
3	43.89±2.09	42.48±2.08	42.75±2.05	58.96± 3.46
4	48.26±3.16	50.22± 4.26	50.41± 3.01	67.87 ±3.27
5	53.93± 1.03	56.65± 4.37	58.29± 4.21	72.23 ±2.20
6	59.27± 4.07	64.19±2.09	64.14± 2.10	79.56± 4.56
7	64.95±2.55	71.46 ±1.67	71.43± 3.16	83.78± 3.70
8	69.62± 4.02	78.63±3.23	77.16± 2.04	89.65± 4.35
9	77.55 ±2.05	84.60± 2.46	83.09± 3.16	96.78± 2.70
10	84.48±2.18	88.14±3.16	89.00± 4.02	102.08 ±4.06
f_2 value	61.56±3.06	68.56±2.79	70.21±2.61	

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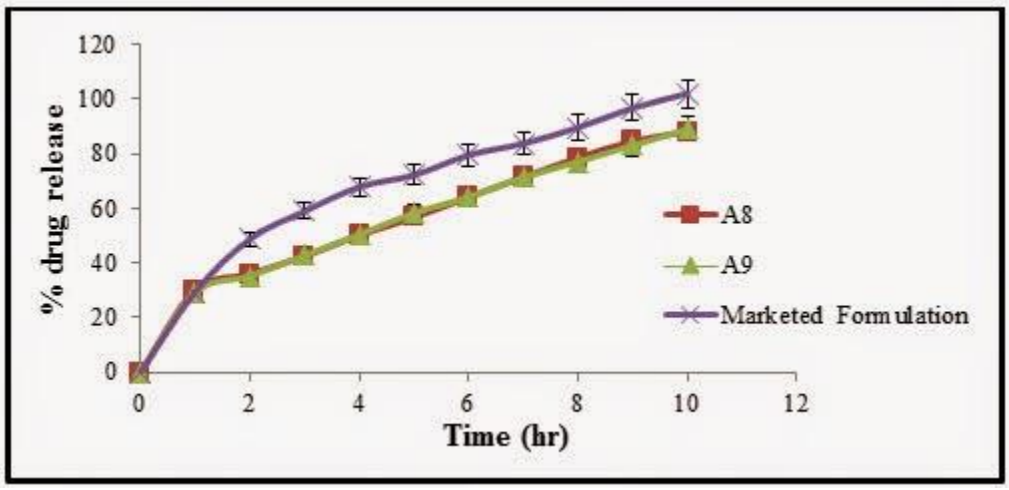

Figure 9.3 : % Drug release of batch A7-A9.

Discussion

According to FTIR and DSC study drug and excipients are compatible with each other.There is no interaction occurs between drug and the polymer when used in combination. Pellets were characterized by their micromeritic properties, such as bulk density, tapped density, compressibility index, hausner's ratio and angle of repose. These all micromeritics properties are optimum.

Now characterization of pellets according to % yield, % assay, % friability. Batch A1, A2 and A3 (5%) batches shows higher friability compare to other batches. From batch A4, A5 and A6 (10%) batches A5 shows less friability, higher % yield and % assay than other batches. Batch A7, A8 and A9 not batter compare to A5.

Now according to % drug release of all batches compared to marketed formulation and calculates similarity factor f_2 value for all batches. Formulation A1, A2 and A3 not proper drug release within 10 hr and their f_2 values were found to be 68.83, 62.43 and 71.68 respectively. From formulation A4, A5 and A6, drug release of formulation A5 was 99.81% at 10 hr which is batter than all other batches and their f_2 values were found to be 67.56, 78.56 and 64.43 respectively. The similarity factor f_2 values for formulation A6, A7 and A8 were found to be 61.56, 68.56, and 70.21 respectively. From above all formulation, formulation A5 shows higher f_2 value than other formulation.

From above discussion it was concluded that formulation A5 was batter than other formulation and it was optimized for further coating process.

Optimization of Process parameters:

Table 14 : Result of optimization of % weight gain:

Batch	Initial weight (gm)	Final weight (gm)	%weight gain
W1	345± 1.21	363±1.51	5.02 %
W2	346±2.15	384± 2.52	10.00 %
W3	345± 2.13	405± 1.95	15.01 %
W4	343± 2.64	429± 2.96	%

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Table 15: Results of % cumulative drug release

	Time (in Hours)	% Cumulative Drug Release			
		W1	W2	W3	W4
In 0.1 N HCl	2	0	0	0	0
In Phosphate buffer pH6.8	1	0	0	0	0
	2	0.92±0.04	0	0	0
	3	1.64±0.16	0.26±0.04	0	0
In Phosphate Buffer pH 7.4	1	29.24±3.27	20.32±2.34	9.63±1.06	4.56±0.26
	2	37.12±2.06	34.13±3.16	15.21±2.14	8.14±1.17
	3	48.23±3.25	42.12±1.82	24.35±2.25	12.31±0.56
	4	61.28±2.17	59.67±4.26	32.13±1.46	20.31±2.63
	6	73.93±1.31	71.05±3.24	48.56±3.21	38.69±3.26
	8	84.65±3.56	82.34±2.65	59.12±3.07	45.76±1.87
	10	94.31±2.67	94.19±4.46	61.12±2.67	59.17±3.72
	12	98.72±3.34	99.73±3.13	79.28±1.65	68.11±2.45
Disintegration test (in 0.1 N HCl)		Disintegration	Intact	Intact	Intact
Problems during Coating		-	-	-	Rough surface

Table 16 : Results of Coating Inlet Temperature optimization

Evaluation parameters	T1 (30° C)	T2 (40° C)	T3 (50° C)
%Weight Gain	10.00 %	10.06 %	10.0 %
Weight variation test (mg)	384±3.01	383±2.51	384±3.58
Disintegration test In 0.1N HCL	Intact	Intact	Intact
Problem during coating	Sticking and Picking	-	Poor elegance and rough surface.

Table 17 :Results of Coating pan speed optimization

Table : Results for Coating pan speed optimization				
Evaluation parameters	**S1(5 RPM)**	**S2(10 RPM)**	**S3(15RPM)**	**S4(20 RPM)**
%Weight Gain	10.00 %	10.06 %	10.02 %	10.0 %
Weight variation test (mg)	384±3.34	385±2.5	384±2.3	384±2.1
Disintegration test In 0.1N HCL	Intact	Intact	Intact	Intact
Problem during coating	Rough Surface	-	-	Rough Surface

Evaluation of Enteric Coated Capsules.

Table 18 : Disintegration study of coated capsule.

pH of solution	Observations
0.1 N HCL	Do not shows breaking of coating layer
phosphate buffer pH 6.8	Shows initially breaking of coating layer
phosphate buffer pH 7.4	Breaking of layer start progressively

Limit: In 0.1N HCL, none of the capsule should show sign of cracks that would allow the escape of the contents or disintegration apart from fragments of coating after 2 hours. In phosphate buffer pH 6.8, all

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six capsules should not disintegrate within 60 minutes. Finally in phosphate buffer pH 7.4 capsules shows breaking of coating layer.

Evaluation of optimized enteric coated batch:

Table 19: Results for optimized Enteric coated batch	
Evaluation parameters	**Value**
%Weight Gain	10.02 %
Weight variation test (mg)	384±2.3
Disintegration test In 0.1N HCL	Intact
Problem during coating	-

Accelerated stability testing of the optimized Batch:

Table 20: Results for Accelerated Stability studies (40ºC and 75%RH)					
	%Cumulative Drug Release				
	Time (in Hours)	**Initial 0 day**	**After 10 days**	**After 20 days**	**After 30 days**
In 0.1 N HCl	0	0	0	0	0
	1	0	0	0	0
	2	0	0	0	0
In Phosphate buffer pH 6.8	1	0	0	0	0
	2	0	0	0	0
	3	0.26±0.02	0.26±0.03	0.28±0.03	0.29±0.04
In Phosphate Buffer pH 7.4	1	20.32±1.32	20.28±1.36	20.15±1.18	20.00±1.26
	2	34.13±1.57	33.14±2.19	32.33±1.53	30.29±1.47
	3	42.12±2.01	41.68±1.95	41.39±2.17	39.25±1.29
	4	59.67±1.86	58.76±2.27	57.69±1.63	56.41±1.83
	6	71.05±1.04	71.03±1.06	70.72±1.29	69.81±1.28
	8	82.34±2.18	82.33±1.85	81.68±1.48	78.69±2.16
	10	94.19±1.45	92.45±2.62	90.55±2.82	89.73±1.87
	12	99.73±2.46	98.86±1.38	98.52±1.63	96.15±1.04
f_2 value			85.73±1.65	79.38±1.27	77.73±1.16
In vitro wash off test for pellets (10 hours)		48± 3.5	48±2.9	47±2.28	45±2.39

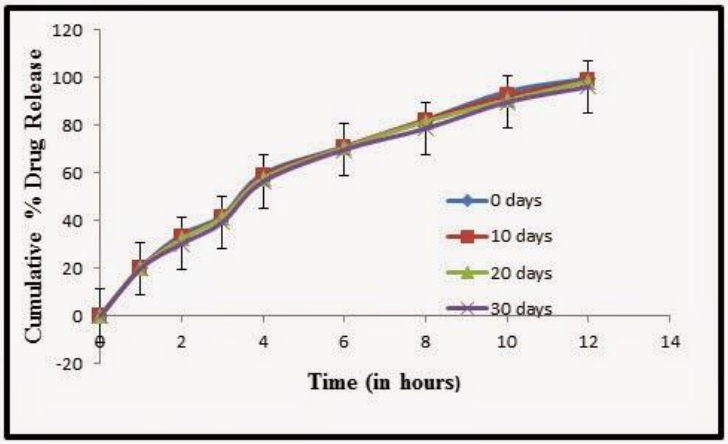

Figure 10: In Vitro Release Comparison at initial time and after stability period.

DISCUSSION

The batch W2 with 10 % weight gain was considered to be optimized as it gave complete

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release at the end of 12 hours in Phosphate buffer pH7.4 and no release was seen in 0.1 N HCl and Phosphate buffer pH 6.8.At 40 °C good coating efficiency as well as smooth surface was observed, and it was kept constant for optimization of pan speed. At 15 rpm pan speed, coating process efficiency was found to be more than other rotating speeds of pan.

From the result of optimized it was seen that spray rate, inlet air temperature and rotating speed of pan had a major effect on capsule coating performances among all others.

The stability study results showed that at the end of 10^{th}, 20^{th} and 30^{th} day, similar values for drug dissolution profile were obtained as at the initial time. The f2 values obtained at the end of 10^{th}, 20^{th} and 30^{th} day were 95.73, 88.38 and 77.73 respectively which indicates similarity in the dissolution profile with the initial profile. So, the formulation was stable and had no significant change in drug release profile, and in vitro wash off test on storage for a long time.

CONCLUSION

Concluded spheronization time, speed and % LOD are significantly influence extrusion spheronization process and may successfully prepare pellets by using it.

Based on the observations, it can be concluded that the formulated capsules filled with pellets and coated with Eudragit S 100 are capable of exhibiting sustained release properties for a period of 12 hrs.

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