RESEARCH ARTICLE

Formulation and Evaluation of Albendazole Microspheres by Ionotropic Gelation method

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ABSTRACT

The objectives of the present studies was to developed Albendazole microparticles by using sodium alginate and tamarind polysaccharide as polymer for colonic delivery of albendazole. microspheres were prepared using TSP and Sodium alginate as blend in different ratios with different calcium chloride concentration as a cross linker by ionotropic gelation. The microspheres were characterized for drug content, percentage yield, particle size analysis and surface morphology. The results of all the physiochemical tests of all formulations were found to be favourable. The swelling index study was shows that low conc. of cross linking agent give higher swelling due to lower degree of cross linking. FT-IR studies indicated that there were no reactions between albendazole, and polymers used. Different formulations of microspheres showed prolonged *in-vitro* release profiles over 12 hours in both stomach and intestinal pH. It was found that the albendazole release in gastric pH was comparatively slow and sustained than intestinal pH. SEM photographs showed that the microspheres were spherical with no visible major surface irregularity. The kinetic study was carried out and the best fitted kinetic model for F-2 batch was Korsmeyer peppas have R value 0.961 and k value was 5.808.

Keywords: Albendazole, tamarind seed polysaccharide, sodium alginate, microspheres.

INTRODUCTION

Microencapsulation is described as a process of enclosing micron-sized particles of solids or droplets of liquids or gasses in an inert shell, which in turn isolates and protects them from the external environment [1].The products obtained by this process, are called micro particles microcapsules and microspheres which differentiate in morphology and internal structure. When the particle size is below 1 mm they are known as nanoparticles, nanocapsules, nanospheres, respectively and particles having diameter between3–800 mm are known as microparticles, microcapsules or microspheres [2]. Particles larger than 1000 mm are known as macroparticles.

Microparticles have been widely accepted as a means to achieve oral and parenteral controlled release [3, 4].

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The microsphere requires a polymeric substance as a coat material or carrier. A number of different substances biodegradable as well as non-biodegradable have been investigated for the preparation of Microparticles [5]. It not only reduces the dose of the drug, reaching to the effective biological sites rapidly but also results in reduced toxicity of the targeting. In the past few years, pharmacists have been focused their research in colloidal drug delivery system/colloidal carriers, like Liposomes, Microspheres and Nanoparticles as a targeting carriers, which has given selective targeting.

Albendazole [6, 7] is an Anthelmintic agent, is mainly used in the management of Helminthiasis. It has biological half-life of up to 8.5 hrs. It is poorly absorbed from the gastrointestinal tract due to low aqueous solubility. The aim of the present work was to develop the Albendazole Microparticles by using sodium alginate [8] and tamarind polysaccharide [9] as a polymer for colonic delivery of albendazole to obtain better pharmacological effect and avoiding side effects associated with albendazole therapy. Tamarind seed polysaccharide [10] (TSP) obtained from the seed kernel of *Tamarindus indica*, possesses properties like

high viscosity mucilage, broad pH tolerance, no carcinogenicity, mucoadhesive nature, and biocompatibility.

MATERIAL AND METHOD

Albendazole was obtained as kind gift sample by Brassica pharma, Boisar. (Maharashtra) India. Tamarind seed polysaccharide was obtained as gift sample by Hari Om Gum Industries, Surat. All other materials and solvents used were of analytical grade.

Formulation of Microspheres:

Preparation of Albendazole loaded TSP-alginate Microsphere.

Ionotropic Gelation Method:

Sodium alginate and TSP aqueous dispersion were prepared separately using distilled water. This dispersion was well mixed with stirring for 10 min. at 1000 rpm using electronic stirrer. Afterwards albendazole was added to this dispersion mixture. The ratio of drug to polymer was maintained 1:1 in all formulations. The final TSP-alginate dispersion containing albendazole was homogenized till it completely mixed together at 1000 rpm. The resulting dispersion were sonicate for 5 min. to debubbling. The resulting dispersion was then added via a 26 gauge needle. The added droplets were retained into $CaCl_2$ solution for 20 minute complete the curing reaction and to produced spherical rigid microsphere. The microsphere were collected by decantation and washed thrice with distilled water and dried at 45^0 C for 12 hrs [11]. The formulation details are given in table no.1.

The preliminary study performed for microspheres formulation with 1:0.5, 1:1, 1:1.5 ratio for drug to polymer. It was found that 1:0.5 ratio for drug to polymer release the drug faster and 1:1.5 ratio for drug to polymer retard the release of drug, while 1:1 ratio for drug to polymer release the drug appropriately so, 1:1 ratio was decided for the final batches of microsphere formulations by using 5%, 10% calcium chloride as cross linking agent.

Table 1: Formulation batches of TSP-Alginate microsphere

Formulation Code	TSP : Sodium alginate	$CaCl_2$
F1	1:1	5%
F2	1:2	
F4	1:1	10%
F4	1:2	

Evaluation of microspheres:-

The microsphere was formulated with above composition were evaluated for following micromeritics properties.

Angle of repose:-

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the microsphere of each formulation was determined by the funnel method [12]. The microsphere was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface, this forms a pile of microspheres on the paper. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation.

$$\mathbf{Tan\theta = H / R}$$

Where, H = pile height, R = radius of pile

Therefore; $\theta = \tan -1 \frac{H}{R}$

Bulk density and tapped density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2g of microsphere from each formula was lightly shaken to break agglomerates if any and then was introduced into a 10 ml-measuring cylinder. It was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2- second intervals. The tapping was continued until no further change in volume was noted. Loose bulk density (LBD) and tapped bulk density (TBD) were calculated using the following formulae [13, 14].

LBD = Weight of the microsphere/volume of the packing

TBD= Weight of the microspheres/tapped volume of the packing

Compressibility index:

The compressibility indices of the formulation blends were determined using Carr's compressibility index formula [11].

$$\text{Carr's compressibility index (\%)} = \frac{(TBD - LBD)}{TBD} \times 100$$

Hausner's ratio:

Hausner's ratio of microspheres was determined by comparing the tapped density to the bulk density using the equation [11].

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Particle size analysis:

The particle size was measured using a stage micrometer, and the mean particle size was calculated by measuring 200 particles with the help of a calibrated stage micrometer. A small amount of dry microspheres was suspended in liquid paraffin (10 ml). A small drop of suspension thus obtained was placed on a clean glass slide. The slide containing microspheres was mounted on the stage of the microscope and diameter of at least 100 particles was measured using a calibrated optical micrometer [14].

Percentage yield:

The percentage yield of different formulations was determined by weighing the microspheres after drying. The percentage yield was shown in table no.12, and percentage yield was calculated as follows.

$$\text{\% Yield} = \frac{\text{Total weight of microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

Drug entrapment:

The various batches of the microspheres were subjected to estimation of drug content [15]. The microspheres equivalent to 100 mg of albendazole, were accurately weighed and crushed. The powdered of microspheres were placed in 100 ml of methanol for overnight. This solution is then filtered through whatmann filter paper. After filtration, use this clear supernatant solution to measured absorbance at 291 nm by using UV-visible spectrophotometer.

$$\text{\% Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Swelling behaviour study [15]:

A 100 mg of albendazole loaded TSP-alginate microspheres were soaked in phosphate buffer pH 7.4 and 0.1N HCL separately for 12 hrs to evaluate swelling behaviour. The swelled microspheres were removed at 1 hr predetermined time interval and weighed after drying the surface using tissue paper. Swelling index was determined by following formula:.

$$\text{Swelling Index} = \frac{\text{Weight of microspheres After swelling} - \text{Dry weight of microspheres}}{\text{Dry weight of microspheres}} \times 100$$

***In-vitro* release studies [16]:**

The *in-vitro* drug released studies of the microsphere formulation containing albendazole were carried out using USP dissolution test apparatus type-II [Electrolab (TDT-08L)]. Weighed amount of microspheres equivalent to 400 mg to the total weight of drug used in microsphere formulation, they were packed in muslin cloth and placed in the basket. The dissolution medium consisted of 900 ml of 0.1N HCL for the first 2 hours, followed by pH 7.4 phosphate buffer for the remaining time period up to 24 hours. The temperature of the medium was maintained at 37±0.5^{0}C. The speed of rotation of the basket was kept at 50 rpm. Aliquots of 10 ml were withdrawn after every hour for a total of 24 hours. The samples so withdrawn were replaced with the fresh dissolution medium to maintain the sink condition throughout the experiment. The collected aliquots were diluted with suitably medium to determine the absorbance at 291 nm for albendazole by using U.V. visible spectrophotometer.

Compatibility study by FT-IR [17]:

Drug-excipients compatibility was studied by using FT-IR spectral analysis. FT-IR instrument (Shimadzu,

Japan) used for the drug-excipients interaction study. A preliminary study was carried out with formulation excipients to determine drug-excipients interaction or compatibility. Drug-excipients compatibility study included Albendazole, sodium alginate and tamarind polysaccharide. Albendazole was uniformly mixed in 1:1 ratio with the excipients and the mixture was placed in glass vials. Vials were sealed by carnauba wax were kept at room temperature and 40°C and 75 % RH. After 30 days sample were withdrawn and observed for change in color and chemical change by recording FT- IR spectrums. The scanning range was 4000 to 400 cm^{-1} .

Compatibility study by DSC [18, 19]:

Differential scanning colorimetry was performed on a Mettler DSC-6220, Japan instrument with a thermal analyzer. Under nitrogen flow of 20 ml/min, sample weights 2 mg for albendazole and 2 mg for drug-polymer mixture were sealed in aluminium pan, and heated at a scanning rate of 10 ºC/min from 40 ºC to 300 ºC. An empty aluminium pan was used as reference.

Scanning electron microscopy:

The scanning electron microscopy was performed on Hitachi high technologies corporation-S4800 type II, Japan. From the formulated batches of microspheres were examined for surface morphology and shape using scanning electron microscope. Morphology details of the specimens were determined by using a scanning electron microscope (SEM). The samples were dried thoroughly in vacuum desiccator before mounting on brass specimen studies. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 20KV during scanning [20].

Kinetic modelling [21, 22]:

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero-order, First-order, Higuchi matrix, and Peppas model using PCP-DISSO -v3 software. Based on the r-value, the best-fit model was selected .

Accelerated stability study: [23]

Accelerated stability study of formulation was carried out as per ICH Guideline to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of microsphere formulation was assessed at 40 ± 2 °C and 75 ± 5% RH as per ICH Guidelines. Microsphere was filled in sealed vial with aluminium foil and stored for 180 days in stability chamber (CIS-24 REMI Instruments Ltd, India). Samples were analyzed for drug content and % cumulative release during time period of 6 months.

RESULTS AND DISCUSSION

FT-IR characterization of albendazole:

IR spectra for albendazole, sodium alginate, tamarind polysaccharide and physical mixture of albendazole are given in fig.1-3. Major functional groups of albendazole (C-H stretching of benzene ring) at 1477 and 1446, (C-H Stretching of alkane) at 2960,(C=C Stretching of aromatic ring) at 1720,(COOH)at1589, (-COO- Bending of Ketone) 1708 (C=N stretching) at 1627 (N-H Stretching of amine) at 3331,(C-N Vibrations) at 1139 can be seen in spectra of individual drugs as well as in spectra of physical mixture. So there is no interaction between albendazole and sodium alginate, tamarind polysaccharide the results of the above study show that various peaks which were observed in official spectra of albendazole matches with obtained spectra of albendazole which confirms about the identity and purity of drug.

The FT-IR spectra of albendazole, sodium alginate, tamarind polysaccharide and mixture of drug-polymer were recorded shown in fig.no.16-19. No any peak observed in IR spectra indicating no chemical interaction between drug and polymers. It also confirmed the stability of drug during microencapsulation process.

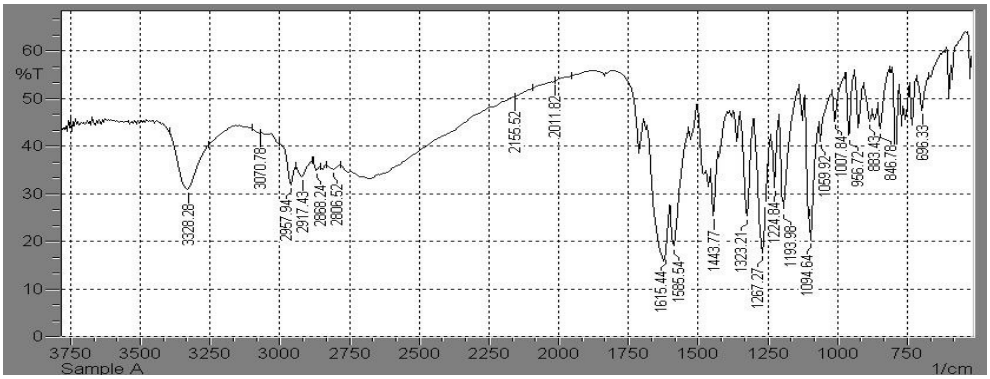

Fig. 1: FT-IR spectra of albendazole

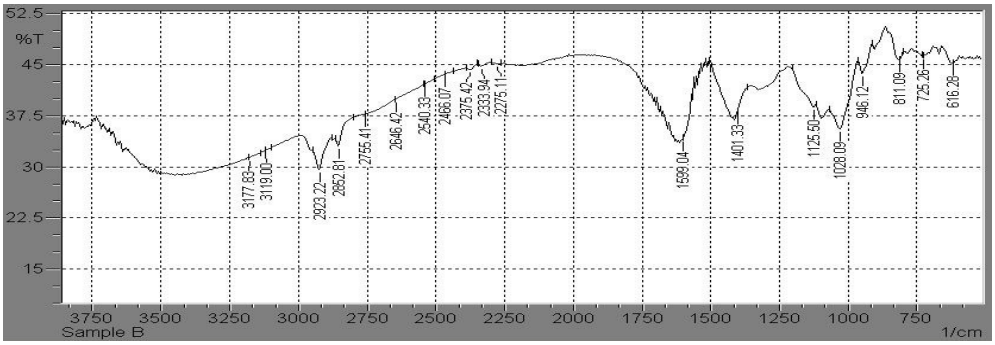

Fig. 2: FT-IR spectra of sodium alginate**.**

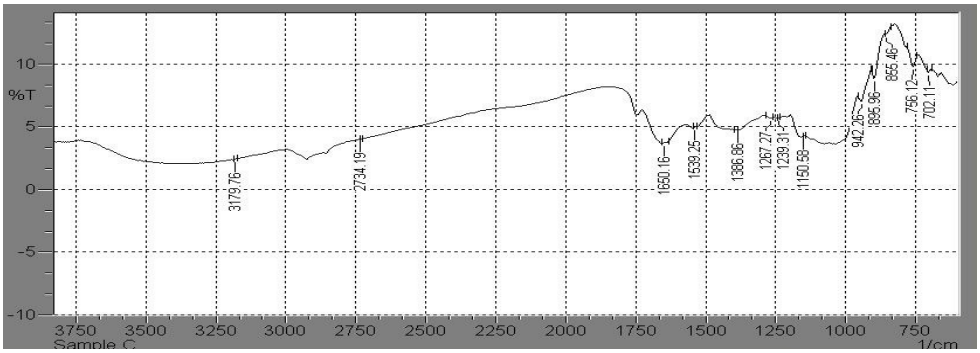

Fig. 3: FT-IR spectra of tamarind polysaccharide**.**

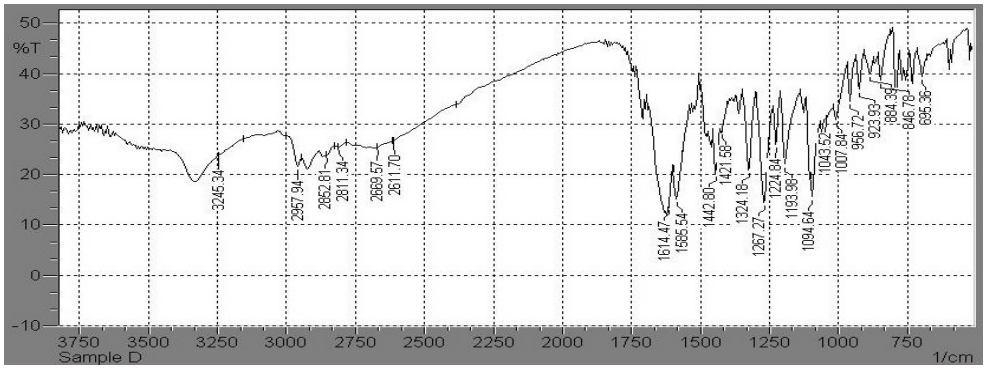

Fig. 4: FT-IR spectra of Optimized Batch

Differential scanning colorimetry:

The differential scanning colorimetry of the albendazole, sodium alginate, tamarind polysaccharide and the drug + polymer was recorded as shown in Fig no.5-8 The DSC thermogram of physical mixture confirmed that there is no

interaction between drug and polymers as shown in fig no 8. It also showed a reduction in intensity of the peak and there was no new peaks found and endothermic to exothermic change not occur. Hence, it was confirmed that there was no interaction between drug and excipients.

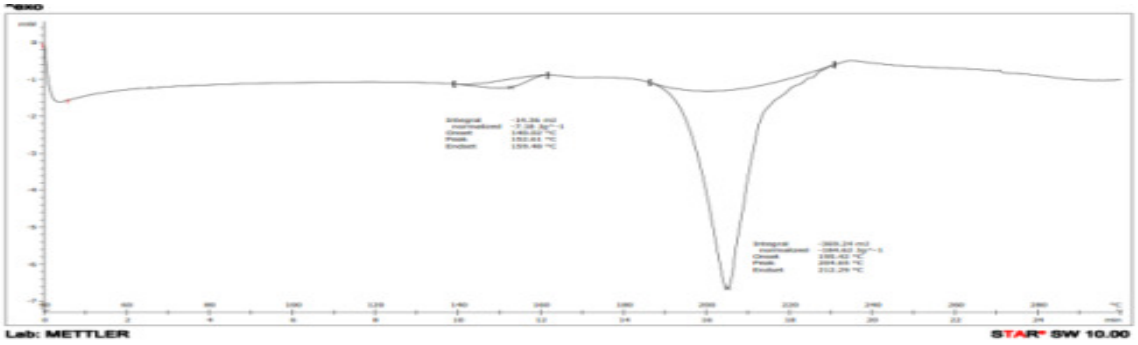

Fig. 5: DSC of albendazole

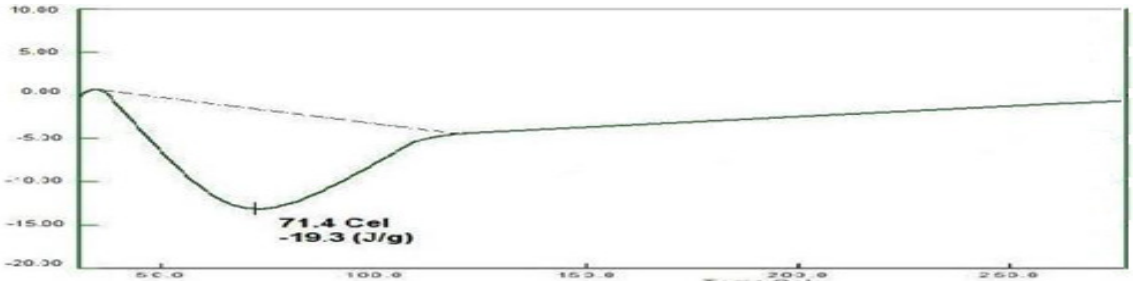

Fig. 6: DSC of TSP

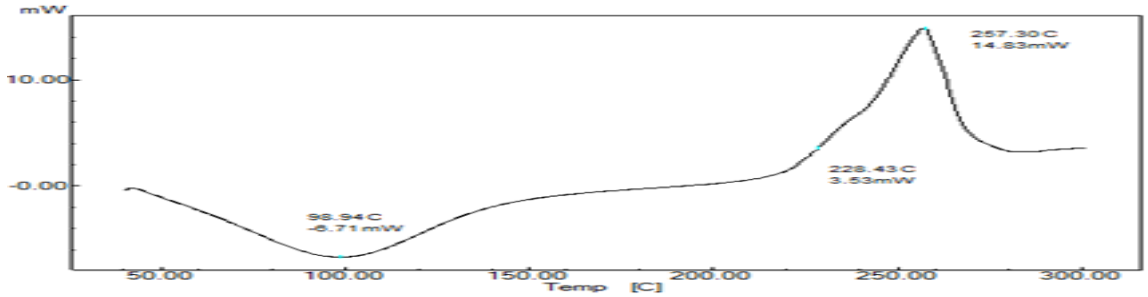

Fig. 7: DSC of sodium alginate

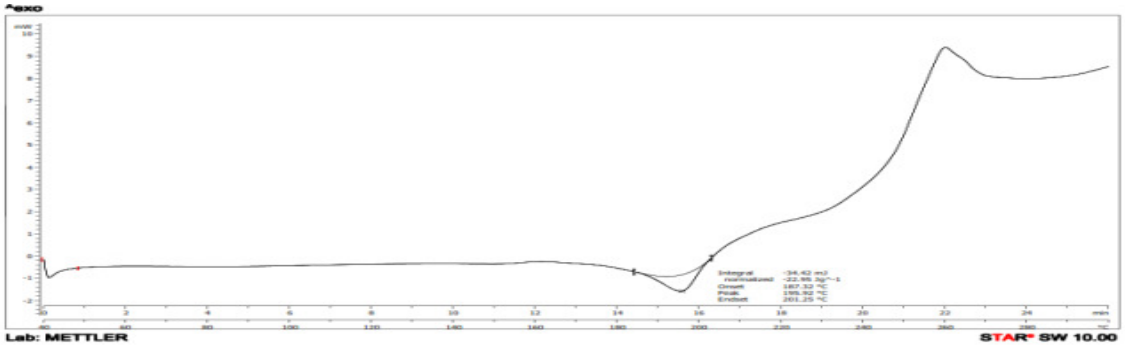

Fig. 8: DSC of drug-polymer mixture

Evaluation of microspheres:

All the formulations show angle of repose value in the range of 23°.61'- 29°.62'. The values for bulk density were found in the range of 00.437 ± 0.03 - 0.476± 0.01 gm/cm^3. Tapped density was found to range from 0.528 ± 0.03 – 0.597 ± 0.03 g/cm^2. Compressibility index were found in the range of 13.60 % - 19.96 %. Respectively, Hausner's ratio was ranging from 1.159-1.316, i.e., all the preparation showed that they had good flow properties.

Table 2: Physical parameters of albendazole Microsphere

Batches	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Compressibility Index (%)	Hausner's Ratio
F1	23.77±0.13	0.467 ± 0.1	0.573 ± 0.03	16.96 ± 0.13	1.205 ± 0.02
F2	28.86±0.99	0.464 ± 0.1	0.550 ± 0.01	14.74 ± 031	1.174 ± 0.01
F3	24.83±1.38	0.455 ± 0.3	0.587 ± 0.01	19.96 ± 0.26	1.257 ± 0.04
F4	23.94±0.51	0.465 ± 0.3	0.547 ± 0.02	14.79 ± 0.18	1.177 ± 0.01

The average particle size of the microspheres was calculated it's in the range between 752-912 µm. The percentage yield of different batches was determined by weighing the microspheres after drying. The percentage yields of different formulation of sodium alginate-TSP microsphere were in range of 62.5 - 74.95 %, the drug entrapment efficiency of different batches of microspheres was determined. The entrapment efficiency was in the range of 67.38% - 87.60%, as shown in table no.3. Drug entrapment efficiency was increased when the crosslinking agent increases. 10 % of $Cacl_2$ shows the maximum drug entrapment as compaired with the 5 % of $Cacl_2$.The drug entrapment efficiencies were increased with decreasing TSP to sodium alginate blend ratios and increasing cross-linking concentrations. This may be due to the high degree of cross-linking.

Table 3: Data for Percentage yield, percentage loading and encapsulation efficiency of microspheres.

Batches	Mean particle size (µm)	Percentage yield (%)	Entrapment efficiency (%)
F1	912.10 ± 0.2	62.5 ± 0.9	67.38 ± 0.3
F2	806.20 ± 1.2	68.12 ± 1.7	74.12 ± 0.12
F3	886.09 ± 1.9	72.87 ± 1.1	76.14 ± 0.14
F4	751.10 ± 0.5	74.95 ± 0.5	87.60 ± 0.23

n = 3

Swelling behavior of albendazole loaded TSP-alginate microspheres was evaluated in simulated gastric medium 0.1N HCL, and intestinal pH 7.4. The swelling index profile of these microspheres in both the pH were shown in fig. no.9.The swelling index of albendazole loaded TSP-alginate microspheres was lower in 0.1N HCL in comparison with swelling index in phosphate buffer pH 7.4. The swelling index of TSP-alginate microsphere in 0.1 N HCL was found to be very low because shrinkage of sodium alginate at acidic medium. This might help to avoid drug release at upper part of gastro intestine hence appropriate amount of drug can be deliver to colonic region.

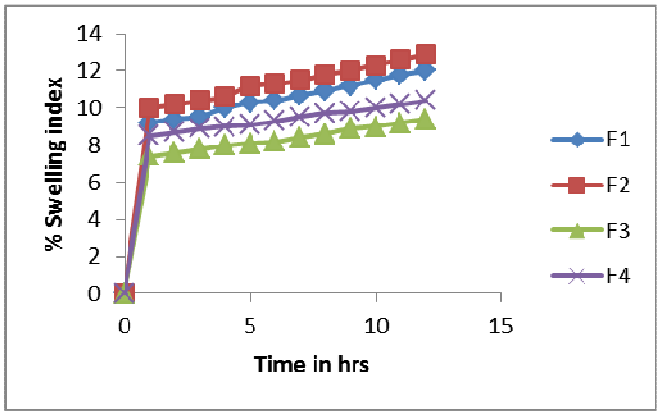

Fig. 9: Swelling behaviour of microsphere at 0.1N HCL

The results of TSP-alginate microsphere for swelling index in phosphate buffer pH 7.4 shows better than at acidic medium. The formulation batch F2 shows higher swelling at basic pH because of hydrophilic properties of TSP and pH dependant properties of alginate. The calcium chloride cross linking was also affect the swelling i.e. higher degree of crosslinking shows lower swelling while at lower degree of crosslinking shows higher swelling of microsphere. F1 and F2 formulation shows 42.4 %, 53.3 % swelling index (Conc. of calcium chloride is 5 %) while F3 and F4 formulation shows 44.6 %, 41 % swelling index (Conc. of calcium chloride is 10 %). The graphical representation for these results shows in fig. no.10.

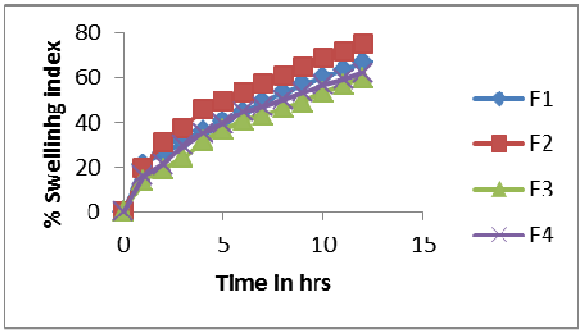

Fig. 10: Swelling behaviour of microsphere at phosphate buffer pH 7.4.

The microsphere formulations of albendazole containing sodium alginate and TSP as polymers, *in-vitro* drug release study was carried out for 12 hrs in 0.1N HCL and pH 7.4 phosphate buffers to all F1-F4 formulated batches at 37^0 ± 0.5^0 C, 50 rpm. The release of albendazole from sodium alginate-TSP microsphere was 8.2 ± 0.63 (F2) and 8.68 ± 0.79(F3) at 0.1N HCL after 2 hrs, while 91.88 ± 0.77(F2) and 76.87±0.50 (F3) at pH 7.4 phosphate buffer after 12 hrs. F2 shows the higher release of drug with maximum swelling index hence it was better formulation. Results of *in-vitro* drug release shown in fig no.11.

The release of albendazole from TSP-alginate microspheres at gastric pH was comparatively slow than intestinal pH. This was due to the shrinkage of alginate at acidic pH (as alginate is pH sensitive), which might slower the drug release from TSP-alginate microspheres. The reason of the higher drug release in phosphate buffer, pH 7.4 was due to the higher swelling rate of these microspheres, while higher the concentration of crosslinking agent could produce high degree of crosslinking thereby lower the drug release from TSP-alginate microsphere formulation.

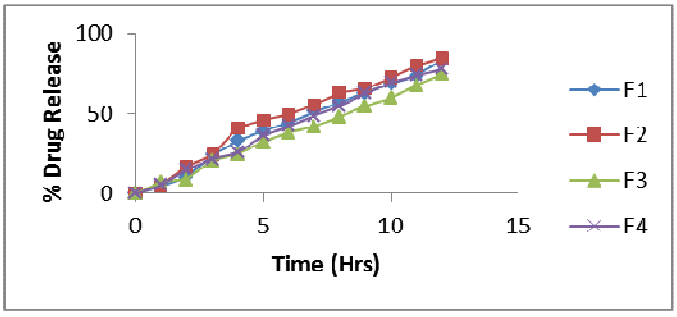

Fig. 11: *in-vitro* drug release profile of formulation

The *in-vitro* release data was applied to various kinetic models to predict the drug release kinetic mechanism and are shown in table no.4. As per PCP-DISSO -v3 software the best fit model for the optimized batch F2 formulation is the Korsmeyer peppas, having R value 0.961 and K value is 5.808.

Table 4: Drug release kinetic modelling

Batch code	Zero order		First order		Matrix		Korsmeyer peppas	
	(R)	(K)	(R)	(K)	(R)	(k)	(R)	(K)
F1	0.816	4.886	0.910	-0.082	0.935	17.464	0.972	7.577
F2	0.843	5.119	0.952	-0.090	0.938	18.257	0.961	5.808
F3	0.867	4.046	0.917	-0.060	0.915	14.227	0.967	5.731
F4	0.825	4.636	0.928	-0.075	0.919	16.388	0.971	5.189

Formulation F2 was the optimized batch of TSP-alginate microsphere which were shows better drug release with higher swelling index, also its don't show any drug-polymer interaction in compatibility study. Hence it was selected for the further accelerated stability study.

Accelerated stability studies (AST) were carried for optimized formulation F2 as per ICH Guideline by exposing it at temperature (40°C) with relative humidity (75%RH) for 180 days and analyzed the sample at the interval of 45 days. The colour, % drug content efficiency and % cumulative release was calculated as shown in 5.

Table 5: Accelerated stability study of F2 formulation

Sr. no.	Days	Colour	Drug content (%)	Cumulative release (%)
			Mean ± SD (n=3)	
1	0	Buff white colour	74.12 ±0.70	84.67±0.45
2	45	No change	74.63±0.20	84.63±0.97
3	90	No change	74.46±0.16	83.63±0.32
4	135	No change	74.35±0.9	83.62±0.78
5	180	No change	74.21±0.12	83.58±0.16

The accelerated stability study for F2 formulation shows that drug content was in between the range of 74.12-74.35 % and its cumulative release was 84.67-83.62 %. The colour of microspheres was also not changed. Hence formulation F2 was stable at specified conditions.

The surface morphology of microspheres were examined by scanning electron microscopy as shown in figures (fig no.28) illustrating the microphotographs of formulation F2. The microspheres were spherical with no visible major surface irregularity. Few wrinkles and inward dents were appeared at the surface of microsphere. It may due to collapse of microspheres during the drying process.

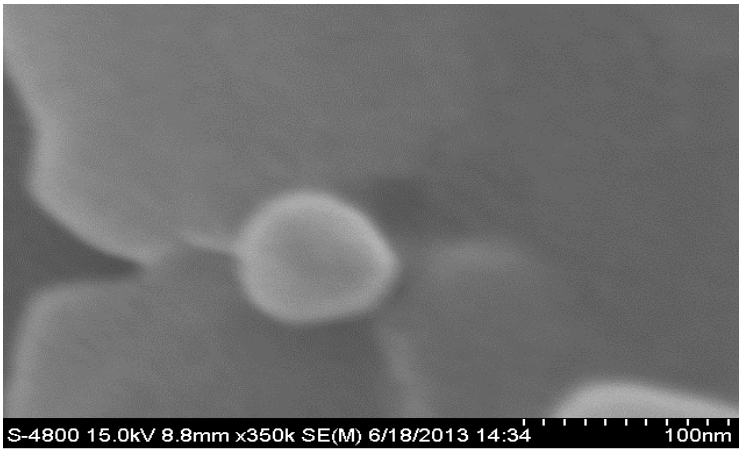

Fig. 12: Scanning electron microphotograph of formulation F-2

CONCLUSION

The F-2 batch microsphere prepared from the albendazole- TSP-sodium alginate as a natural polymers in that the drug-polymer ratio is, 1:1 and 5%, 10% concentration of calcium chloride was used as crosslinking agent. Albendazole microsphere F1 & F2 formulation releases the maximum drug (83.76 %, & 87.67 %) for 12 hrs. F2 Formulation has maximum swelling capacity than F1 so it releases the maximum amount of drug. Hence the F-2 formulation is optimized formulation on the basis of release pattern. The kinetic study was carried out and the best fitted kinetic model for F-2 batch was Korsmeyer peppas have R value 0.961 and k value was 5.808.

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