ORIGINAL ARTICLE

ENTRAPMENT OF ANDROGRAPHOLIDE IN CROSS-LINKED ALGINATE PELLETS: I. FORMULATION AND EVALUATION OF ASSOCIATED RELEASE KINETICS

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ABSTRACT

Andrographolide, the "King of bitters" requires high doses in the form of an extract (33.3%w/w) to be used as a hepatoprotectant. Since a large dose of this herb is known to cause gastric distress, vomiting, loss of appetite and nausea on regurgitation, it was thought of to convert the drug itself into a bitterless micropellet. The technique of ionotropic gelation of sodium alginate with calcium ions with subsequent drug entrapment was employed. The optimization of process parameters like the bore diameter of the needle, % concentration of sodium alginate, method of drying, drying time and temperature, time of contact of the micropellets in calcium chloride solution and concentration of calcium chloride to be used for the gelation were undertaken. The micropellets were finally prepared by adding 2.5%w/v of sodium alginate into a 2%w/v solution of calcium chloride solution using 20-guage flat tip needle and dried using a hot air oven at 60^{o}C for 6 hrs. The so formed pellets were completely bitterless and released the andrographolide preferably away from the stomach. Pellets with varied drug: polymer ratio (1:2, 1:1 and 2:1) were prepared accordingly and analyzed for release kinetics. Release studies showed only about 15% release upto 4 hrs in pH1.2 and pH4.0 respectively and released the remaining in pH 7.4.The data obtained in the dissolution studies was fitted into various mathematic models defining kinetics of drug release like the zero-order rate equation, first-order rate equation, Hixson-crowell, 2/3rd rule, Korsemeyer-Peppas, Baker-lonsdale, Higuchi, Weibull, Ford and Hopfenberg Equation. The release kinetics of andrographolide from the alginate pellets was found to be best described by the korsemeyer-peppas equation which provided n values ranging from 1.0-1.47 with good linearity of the best-fit line (R^2=0.9973). In conclusion, andrographolide can be easily converted to bitterless multiple unit dose oral delivery systems with good entrapment efficiency and a maximum release of 86% by utilizing the technique of ionotropic gelation.

Keywords: Andrographolide, ionotropic gelation, modulated temperature differential scanning spectroscopy, FT Raman spectroscopy, XRD, FTIR.

INTRODUCTION

Andrographis paniculata (burm. f) Wall. ex Nees (Syn. Justicia Paniculata Burm F, A. Subspathulata CB Clarke), a well-established hepatoprotectant (Indian Herbal Pharmacopoeia, 2002) needs to be exploited for its potential by using it as a monoherbal rather than in a polyherbal product. It being popularly known as "king of bitters" often poses disadvantages of nausea on regurgitation when administered orally in large doses. This study was an attempt to mask the bitterness of andrographolide and prevent its release in the stomach. The major formulation problem encountered while masking the taste of a high dose drug is the limited use of excepients. So our endeavor was to convert the drug itself into a bitterless micropellets. Further formulation into a multiple unit dosage form offered advantages like low incidence of localized gastrointestinal disturbances, better mixing of the drug in the G.I.Fluids that in turn gives rise to improved bioavailability etc (Sellassie 1989). The alginate micropellets obtained by ionotropic gelation with counter ions like calcium have been conventionally used to achieve sustained release or for stability improvement by site-specific delivery of drugs sensitive to acidic pH (Iruin et al., 2005). The hydrogels of alginate produced by cross-linking with calcium ions have also been used successfully as scaffolds for tissue engineering (Catherine and Peter, 2001). We have exploited the mechanism of ionotropic cross-linking of alginate with subsequent drug entrapment to make the andrographolide unavailable to the taste buds and also release the drug specifically away from the upper part of GIT.The micropellets were prepared by ionotropic gelation of sodium alginate with calcium ions in which the drug andrographolide was entrapped. The micropellets thus obtained were completely bitterless in taste.

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Part I of this paper deals with formulation details including optimization of process parameters, evaluation of release kinetics supplemented with mathematical model fitting. While part II involves physico-chemical characterization of the micropellets to study the mechanism of pellet formation.

The formulated pellets were evaluated for release properties in pH1.2, pH 4.0 and pH 7.4. The data obtained from the release profile was analyzed using mathematical models to determine the release mechanisms.

MATERIALS AND METHODS

The following materials were used: *Andrographis paniculata* extract 33.3%w/w and Andrographolide 99.8% (Natural Remedies pvt. ltd, Bangalore, India), Sodium alginate (Loba Chemie Ltd., Mumbai, India), Calcium chloride (anhydrous) (Loba Chemie Ltd., Mumbai, India), Sodium lauryl sulphate (gift sample from Jagdale Scientific Research Foundation,Bangalore, India). All chemicals and reagents used were of analytical grade and were used without any further purification as such.

Optimization of bore diameter and % concentration of sodium alginate solution

The viscosity of the colloidal solutions of sodium alginate increases with its concentration.1%, 2%, 3% and 4% solutions of sodium alginate were prepared and extruded through needles of #18, #20 and #22 gauge. The beads were collected from the Calcium chloride solutions after sufficient time for reaction to complete and dried at 60^{o}C for 8hrs.

Optimization of method of drying, drying time and temperature

A 2.5% solution of sodium alginate was prepared and extruded through gauge #20 needle into the calcium chloride solution. After sufficient time for completion of reaction, the beads were collected by filtration and repeatedly washed with distilled water to remove unreacted calcium chloride present on the surface of the pellets. These pellets were divided into three batches. The first batch was subjected to drying in a hot air oven at 60^{o}C for 2hrs, 5hrs and 8hrs.The second batch was air dried for sufficient time till no change in weight was observed and the pellets were free flowing. The third batch was subjected to vacuum drying at a temp of 25^{o}C for 48 hrs at 15psig. The fourth batch was subjected to drying using a microwave (600W) for duration of 180 mns. The different batches produced were evaluated by visual inspection, by SEM for sphericity, surface, size of the pellets and for Disintegration Time.

Optimization of time of contact of the beads in calcium chloride solution

This study was conducted with the assumption that the time of contact of the calcium alginate pellets in calcium chloride solution may have some effect on the sphericity and rigidity of the swollen pellets. Blank pellets were prepared using 2.5% solution of sodium alginate in 2% calcium chloride solution and were allowed to react for different intervals of time like 15 minutes, 30 minutes, 60 minutes and overnight.

Estimation of viscosity of alginate solutions after incorporation of drug

The viscosities of drug loaded sodium alginate solutions were determined in-order to serve as an in-process control parameter during manufacturing. The viscosity of a blank sodium alginate solution in water (2.5%) was first determined using Brookfield DV-E viscometer. Then drug was incorporated in a ratio of 1:1, 1:2 and 1:3 in 2.5% sodium alginate solution and their viscosities were determined similarly.

Optimization of concentration of calcium chloride solution used for ionic gelation of sodium alginate

Atomic absorption spectroscopy and disintegration test were used to arrive at an optimized concentration of calcium chloride to be used further in the manufacture of micropellets.

AAS was performed on the micropellets to find the residual sodium content in the micropellets. Sufficient quantity of the micropellets were digested in conc. HNO_3, the resulting clear solution was analyzed using Hollow Cathode Lamp for the residual sodium content using Atomic Absorption Spectrophotometer 4139, Electronics Corporation of India Limited.

Method of preparation

A 2.5% sodium alginate solution was prepared by dissolving the polymer in deionised water. Accurately weighed amounts of the extract of *Andrographis paniculata* (33.3%w/w of andrographolide) was dispersed into the alginate solution with constant stirring according to the ratio required [drug:polymer =1:2, 1:1 and 2:1 coded as F1, F2 and F3 respectively]. Thus obtained dispersions were sonicated for 20 minutes to remove air bubbles entrapped during stirring. These dispersions were added drop wise into 2% solution of calcium chloride through a 20-guage needle with stirring using a magnetic stirrer. The formed pellets were allowed to cure in the calcium chloride solution for about 30 minutes. The pellets were then decanted and washed repeatedly with about 1000ml of deionised water in three increments. The pellets were then dried in a hot air oven at 60^{o}C for 5 hrs.

Drug entrapment studies

100mg of the drug loaded pellets from the different batches F1, F2 and F3 were taken in 500ml of phosphate buffer pH 7.4 along with 1% S.L.S in 1000ml conical flasks and stirred continuously using magnetic stirrers till the pellets burst completely. Aliquots were taken and required dilutions were made up with methanol and

estimated by HPLC (Indian Herbal Pharmacopoeia, 2002) using Lachrom Interface L7000, Autosampler L 7200, Pump L7110, UV Detector L 7400 from Merck Hitachi, India.The drug entrapment capacity was calculated using the following formula

Drug entrapment capacity (%) = (AQ / TQ) X 100

Where AQ is the actual quantity of the drug present in the micropellets and TQ is the 100% theoretical quantity of the drug that must be present in the micropellets i.e. initial loading dose.

Disintegration test

Disintegration studies (Roland and Ornlaksana, 1989) were carried out in 50ml of buffer media pH1.2 and pH 7.4 taken in 100ml conical flasks. A maximum of 5 pellets were taken in each trial and stirred using magnetic stirrer maintained at 37°C, 25 rpm. Each batch of formulation F1, F2 and F3 was run in triplicate and the time taken for all the 5 pellets to disintegrate leaving behind polymer in the soluble form and drug in the insoluble form was noted as the disintegration time.

Equilibrium swelling studies

Equilibrium swelling is one of the most important properties of a hydrogel that directly influences the rate of water sorption, the permeability to drugs and the mechanical strength of the gel. It also affects the biocompatibility of the gel making it customary to include equilibrium-swelling studies in the evaluation of a swelling-controlled hydrogel systems (Hubbell, 1996). Equilibrium swelling can be experimentally calculated by determining the swelling ratio.

100mg of the micropellets of the different batches F1, F2 and F3 were taken in 500ml of simulated G.I. fluids (pH 1.2, pH 4.0 and pH 7.4) using the USP dissolution apparatus with the paddle assembly at 37°C and 50 rpm. The micropellets were periodically removed, blotted with filter paper and the change in weight was measured. The maximum swelling in pH 1.2 was noted and the same pellets were then transferred to the next medium i.e. pH 4.0 and successively to pH 7.4. The final weight noted was in pH 7.4 after a time period of 4 hrs. The swelling ratio was calculated using the following formula,

$$SR = (W_e - W_o) / W_o$$

Wo is the initial weight of the dry micropellets and W_e is the weight of the swollen micropellets after equilibrium swelling in the respective media. Each trial was repeated thrice and the average value ± S.D was noted as the swelling ratio.

In vitro release studies

The release of andrographolide from the micropellets was studied using the USP dissolution paddle assembly (DA-6D, Veego Scientific Devices.) at a temperature of 37 ± 0.5°C and 50 rpm. The media used were buffers of pH 1.2 for 2 hrs, pH 4.0 for the next 2 hrs and pH 7.4 for the last 4 hrs of the 8 hr study. 5ml aliquots were withdrawn at appropriate time intervals and assayed using H.P.LC. All the trials were performed in triplicate.

Dissolution data analysis and model fitting

The *in vitro* release data was analyzed to determine the mechanism of drug release by fitting the data into ten equations defining release kinetics. Microcapsules/ Microparticles are often irregular in shape. So the conventional models based on regular geometry like spherical/cylindrical often show poor fit for release data. So mathematical approaches like Zero-order, First order, Hixson-Crowell, Higuchi, Korsemeyer-Peppas, Weibull, Ford, Baker-Lonsdale and Hopfenberg equations as indicated in Table V were used to analyze the release profiles obtained at pH 1.2, pH 4.0 and pH 7.4.

RESULTS AND DISCUSSION

Optimization of bore diameter and % concentration of sodium alginate solution

As the bore diameter of the needle increased the particle diameter also increased. Further increase in bore diameter disturbed the sphericity of the micropellets as observed under an optical microscope. #20 gauge needle was chosen as it gave smaller, and more spherical pellets. The lower concentrations of alginate solutions (1%, 2%, 3%) passed freely through all the three gauge needles, but frequent blockage was encountered through gauge #20 and #22 with the 4% solution. The blank pellets prepared using 1% solution of sodium alginate lost their sphericity on drying, so 1% solution and 4% were eliminated from further studies. The 2% and 3% solutions showed equal ease in extrusion from the needle and showed similar shape and contour under the microscope. So an average of both i.e. 2.5% solution was decided upon to be maintained during further studies.

Optimization of method of drying, drying time and temperature

Scanning electron microscopy

Figure 1 represents photomicrographs of micropellets dried using vacuum at 60°C.

In the figs. a, b, c and d represent micropellets captured in a group, on low magnification, on high magnification and that of an individual pellet respectively. A number of large crystals of drug were noticed on the surface of pellets on high magnification. The drug may have migrated from the core during drying along with water. These pellets had residual bitterness when compared to the absolutely bitterless pellets obtained by the other three methods. The surface was however more consolidated with less cracks when compared to microwave and air-drying wherein folds of polymer were noticed. The tailing

noticed in a few pellets is due to variations in the manual pressure applied during formation of the pellets.

Figure 2 represents photomicrographs of micropellets dried using a microwave. The pellets were found to be more uniform and spherical compared to other methods of drying. Although the drug on surface was comparatively less, cracks in the polymer surface were more compared to vacuum drying as observed in pictures obtained on low magnification of individual pellets. Figure 3 represents photomicrographs of micropellets that were air-dried. The pellets were uniform. Few crystals of drug and a few pores were noticed on high magnification.

Figure 4 represents photomicrographs of pellets dried using a hot air oven at 60^{o}C. The pellets were spherical and uniform. A number of crystals of drug were noticed on the surface. The surface was however more consolidated with almost nil cracks and pores and minimum folds. The disintegration times of the four batches are given in the table 1. It was noticed on visual inspection that pellets started shrinking in size as drying progressed and oven drying at 60^{o}C for 2 hrs was insufficient as the pellets were still moist. The pellets were completely dry in 5 hrs and further drying for 8hrs did not produce any significant difference in weight variation or particle size. So drying at 60^{o}C for 5 hrs was considered a good option for drying. The second batch dried in air took approximately 36 hrs to dry to free flowing condition. The Third Batch by vacuum drying produced slight bitterness compared to the wet and swollen pellets, which were completely bitterness free. This could possibly be due to the -migration of the drug from the core along with the moisture on application of vacuum. The Fourth batch dried using a microwave oven gave equally good, spherical, dried pellets as the first batch using the hot air oven. The choice of using a hot air oven for drying at 60^{o}C for 5 hrs was decided based upon the results of disintegration test, wherein the dis-integration time was comparatively lower than the rest. The availability and economy of the conventional hot air oven also contributed to its selection.

Optimization of time of contact of the micropellets in calcium chloride solution

The pellets in contact with calcium chloride for 30 minutes were more spherical compared to 15 mins batch as visualized under an optical microscope. But there was no difference in sphericity of the rest of the two batches (60 min and overnight). On slightly compressing the wet pellets between the fingers, certainly the pellets were more rigid compared to previous batches. The rigidity and sphericity of the pellets kept in contact for 30 mins was good and as the probability of the drug leaching out into the solution when kept for too long was high, it was decided to keep the pellets in contact with calcium chloride solution for 30 mins.

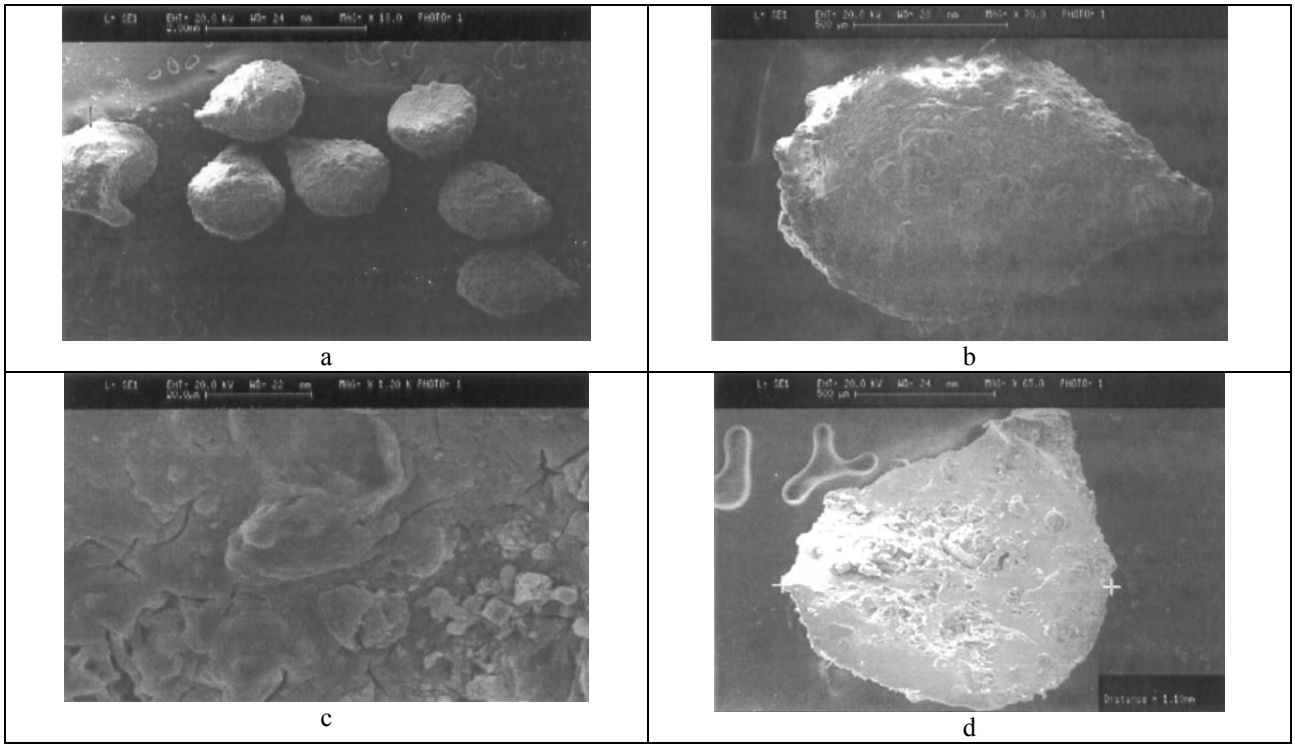

Fig. 1: Scanning Electron Microscopy Micrographs of micropellets dried using vacuum at 60^{o}C a, b, c and d represent micropellets captured in a group, on low magnification, on high magnification and an individual pellet respectively.

Estimation of viscosity of alginate solutions after incorporation of drug

A decrease in the viscosity of the sodium alginate solution was seen on incorporation of drug as seen in table 2. The stated viscosities can be used as in-process control values during manufacture of the micropellets using the respective ratios of drug and polymer.

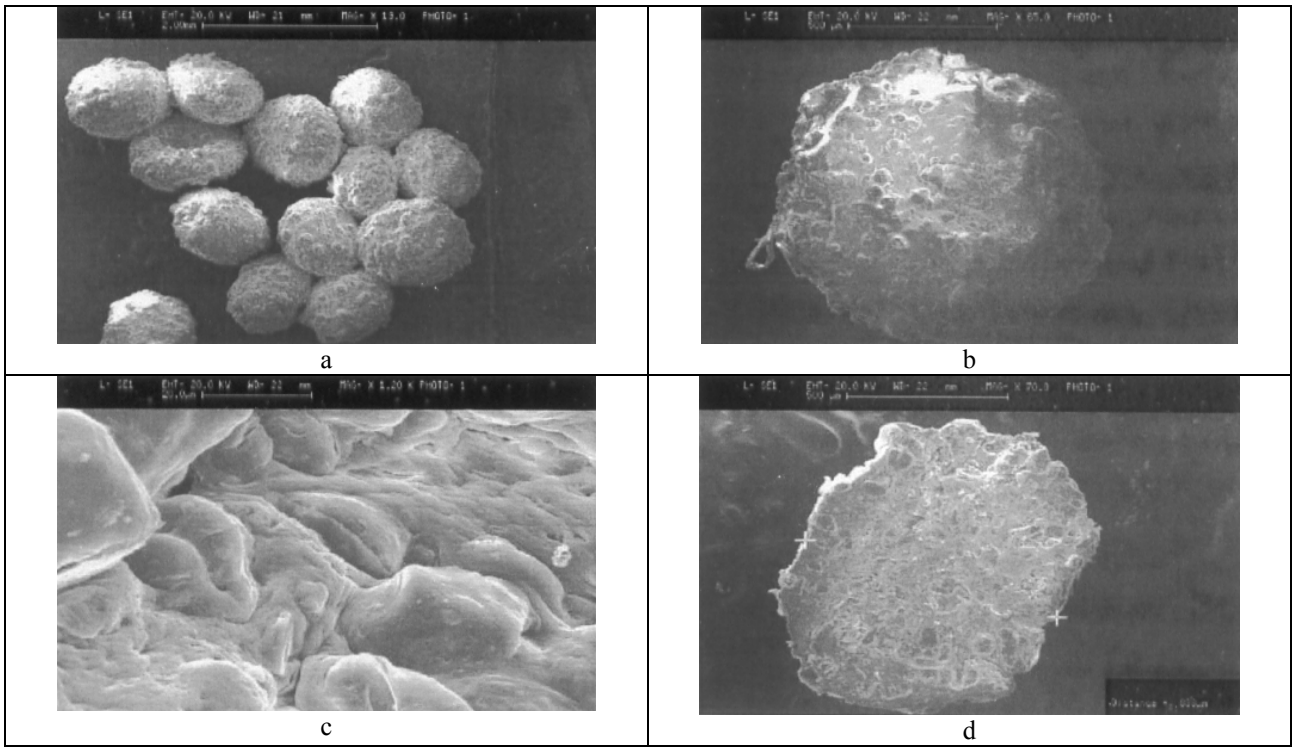

Fig. 2: Scanning Electron Microscopy Micrographs of micropellets dried using microwave oven a, b, c and d represent micropellets captured in a group, on low magnification, on high magnification and an individual pellet.

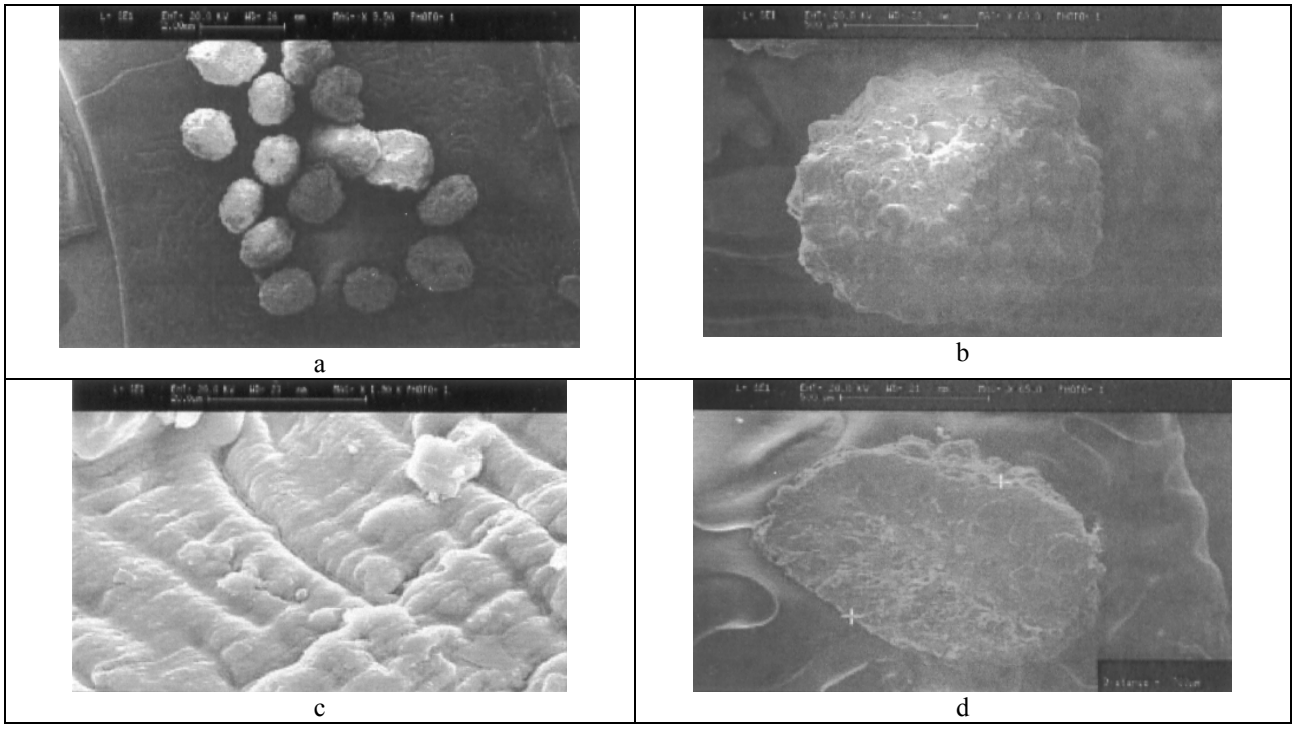

Fig. 3: Scanning Electron Microscopy Micrographs of micropellets air dried a, b, c and d represent micropellets captured in a group, on low magnification, on high magnification and an individual pellet

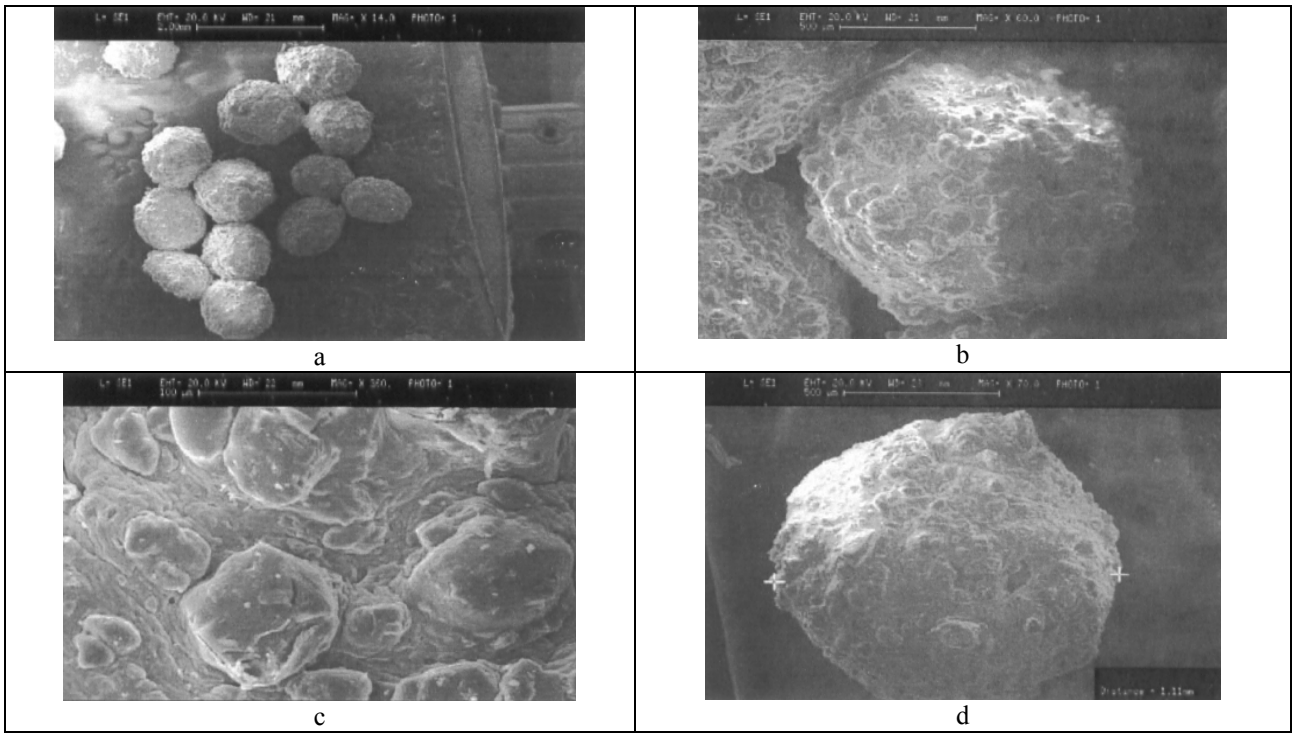

Fig. 4: Scanning Electron Microscopy Micrographs of micropellets dried using hot air oven at 60^0C a, b, c and d represent micropellets captured in a group, on low magnification, on high magnification and an individual pellet respectively.

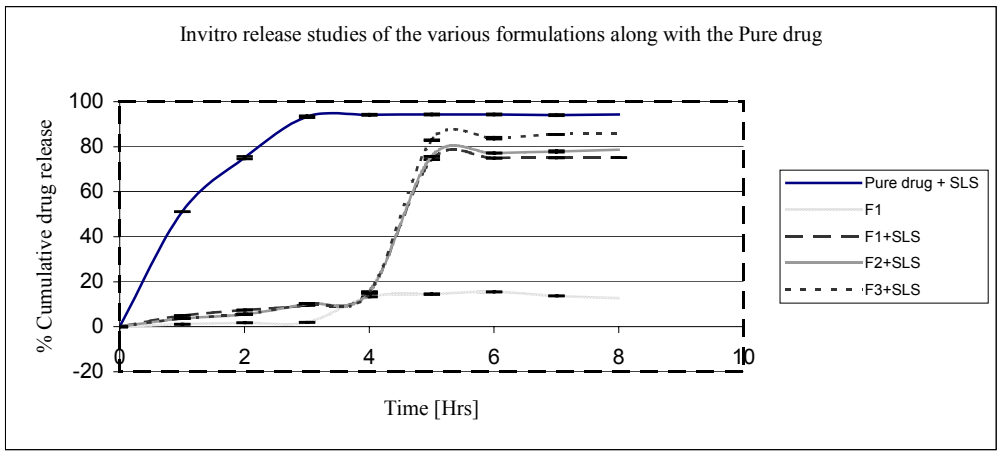

Fig. 5: Dissolution profile of the pure drug and that of the various formulations. All values are mean ± SD.

Optimization of concentration of calcium chloride solution used for ionic gelation of sodium alginate

The micropellets prepared using varying concentrations of calcium chloride that were estimated by A.A.S showed very little variation in the residual sodium content as shown in table 3. Our aim of determining the optimum concentration of calcium chloride required to complete the complexation was not accomplished with the A.A.S studies. However the disintegration studies demonstrated a clear difference in the disintegration times of the different micropellets. The disintegration of micropellets prepared in 2% calcium chloride concentration was comparatively faster. Based on the comparative fast disintegration and with a view of utilizing minimum calcium chloride required to complete complexation, it was decided to use 2% calcium chloride solution in further studies.

The disintegration times of the micropellets increased with increased polymer concentrations. Increased polymer concentration led to increased viscosity of the polymeric matrix and increased cross-linking in turn resulting in stronger pellets which led to longer times for disintegration. The equilibrium swelling studies showed

an increase in the equilibrium swelling with increase in polymer concentration. There was minimum swelling in pH 1.2 due to minimum solubility of the polymer sodium alginate in pH 1.2. However there was appreciable increase in swelling in pH 4.0 at the end of 2 hrs and in pH 7.4. This was due to increased solubility of the polymer in basic pH leading to relaxation of the cross-linked polymeric network. This relaxation will reflect in an increase in the release of drug from the matrix as noticed in the dissolution profiles of the micropellets. The entrapment efficiency of drugs into the micropellets was high, except for a small amount of the drug, which was lost into the external phase. Mechanically strong pellets with a drug content upto 98% can be prepared by using this simple, easy, economic and fast method.

The drug release from the micropellets of the different formulations is shown in fig. 5. The drug being very

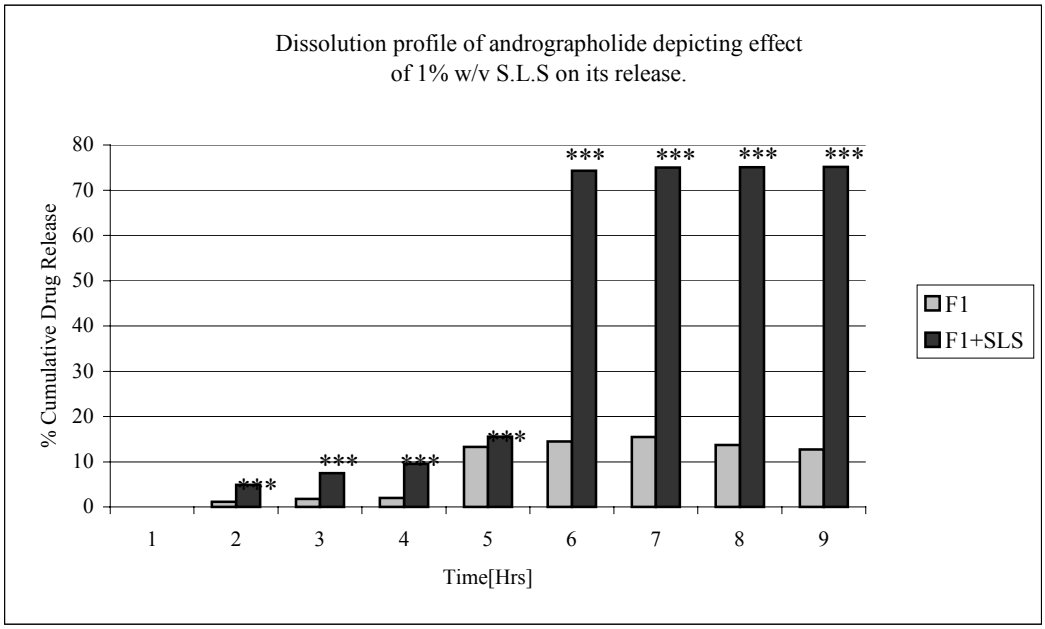

Fig. 6: Dissolution profile of andrographolide from alginate micropellets depicting effect of 1% w/v S.L.S on its release. All values are mean ± SD. *** indicates P <0.001 when compared with F1.

Table 1: Disintegration times of micropellets formulated using different methods of drying

Serial No.	Method of drying	Disintegration time*(minutes)
1	Hot air oven dried (8 hrs)	115
2	Air dried (approx 36 hrs till free flowing)	123
3	Vacuum dried (25^{o}C, 15psig, 48hrs)	172
4	Microwave dried (600W) for 3hrs	118

*Disintegration times given are an average of 3 trials.

Table 2: Viscosities of Solutions of sodium alginate blank and after incorporation of andrographolide.

Serial No.	Name of sample	Viscosity (cp), spindle #S63
1	Blank sodium alginate solution (2.5%)	1793(RPM50, 74.7% torque)
2	Drug incorporated (1:1)	535(RPM 30, 53.5% torque)
3	Drug incorporated (1:2)	541(RPM 30, 54.1% torque)
4	Drug incorporated (2:1)	1471(RPM 50,61.1% torque)

Table 3: Values of residual sodium and disintegration times of pellets prepared using varied calcium chloride concentrations.

Conc.of calcium chloride solution (%)	Residual sodium (%)	Disintegration time (min)
2%	1.55	115
3%	1.56	130
4%	1.52	170

Table 4: Data for the drug entrapment efficiency and disintegration times of the three formulations

Formulation code	Disintegration time (minutes)	Equilibrium swelling ratio	Drug entrapment capacity (%)
F1	126.4	7.78	94.89
F2	139.7	8.69	91.83
F3	97.1	6.73	97.50

Table 5: Release parameters of the formulations for 0-8th hour study

Formulation Code	Zero order		First order		Higuchi		Hixson-Crowell		Baker Lonsdale		2/3rd rule	
	R^2	$K_0(h^{-1})$	R^2	K_1 (h^{-1})	R^2	K_H (h-1/2)	R^2	$_{HC}(h^{-1/3})$	R^2	k	R^2	k
F1	0.8239	11.846	0.7981	0.0972	0.6907	33.043	0.8767	0.1115	0.7669	0.0250	0.8669	0.1215
F2	0.8308	12.436	0.8116	0.1067	0.6904	34.559	0.8948	0.1163	0.7839	0.0286	0.8740	0.1271
F3	0.8234	13.618	0.8071	0.135	0.6809	37.75	0.8937	0.1206	0.7836	0.0377	0.8665	0.1354

Formulation Code	Korsemeyer-Peppas			Ford			Weibull		Hopfenberg	
	R^2	n	K_{kp} (h^{-n})	R^2	n	K_f (h^{-n})	R^2	α	R^2	k
F1	0.9221	1.0371	0.0343	0.8192	0.0002	72.276	0.7864	0.0801	0.9647	0.0126
F2	0.9996	1.4750	0.0198	0.9887	0.0008	72.3602	0.7210	0.0799	0.8166	0.0640
F3	0.9973	1.4066	0.0214	0.9577	0.0009	72.2936	0.7864	0.0801	0.8104	0.0763

slightly soluble in water showed poor solubility in the buffer media as a result of which we had to use 1% S.L.S in the media to aid the dissolution of the andrographolide. This fact is reconfirmed as seen in fig 6 in the release profile of F1 (Drug: polymer: 1:2) used as such and along with 1% S.L.S wherein the latter showed significantly greater ($p<0.001$) release of andrographolide.

The dissolution data of the three formulations F1, F2 and F3 fitted into the various kinetic models gave a linear relationship with r^2 values as depicted in tableV. The optimized formulation F3 is considered here for discussion. The zero-order plot and the first order plot gave r^2 values of 0.8234 and 0.8071 describing the relationship of drug release with concentration of drug. Similar was the case with Weibull and Higuchi plots which showed low values for r^2 as seen in the table 5. Applying the power law to the first 60% of the dissolution data demonstrated good linearity with r^2 values of 0.9973 and n=1.4. As per the rule, n>0.89 is suggestive of super case II transport.

Pillay and Fassihi, 1999 proposed negligible erosion for calcium alginate pellets based on the low erosion constant values obtained in their study using the Hopfenberg model. Considering n=3 in the Hopfenberg equation, the data in the present study also demonstrated poor linearity (r^2 =0.8596) but this can be possibly attributed to absence of perfectly spherical shape of the pellets which is a prerequisite for obtaining best –fit for this equation. On contrary to the proposition by the above authors, a gradual erosion of the micropellets to a considerable extent was observed during dissolution in the present study. So the Hixson-Crowell Cube Root Law which indicates a change in surface area with progressive dissolution of the matrix with time was applied. This demonstrated poor fit (r^2 =0.8937) which was again contradicting our observation. So the same equation was applied in two parts i.e., 0-4^{rth} hour study and 4^{rth}-8th hour study since alginate is insoluble in acidic pH and more soluble in pH>7.0.As assumed, best fit with r^2 =0.9976 (K_{hc}=0.0134), 0.9708 (K_{hc}=0.0038) and 0.9490 (K_{hc}=0.0038) for F1, F2 and F3 respectively was obtained for the 4^{rth}-8th hour study where erosion of matrix was maximum.

CONCLUSION

Andrographis paniculata extract (33.3%w/w) can be successively entrapped into alginate matrix in a ratio of 2:1 drug: polymer to give bitterless micropellets with a maximum of 86% drug release in 8hrs. Since the micropellets preferentially release about 85% of andrographolide at pH 7.4 i.e. away from the upper part of G.I.T, the problems of vomiting, loss of appetite and nausea on regurgitation can be avoided. Drug release kinetics of the micropellets is best described by the Korsemeyer-Peppas equation, which showed good linearity with n values of 1.47 suggesting a super case II transport. The kinetics as described by the Hixson-Crowell Cube Root equation also demonstrated good linearity when applied to the dissolution data in pH 7.4. The kinetics can be summarized as being indicative of relaxation and diffusion in pH 1.2 occurring simultaneously followed by diffusion and erosion at pH 4.0 and 7.4. Although the various models are quite self-explanatory, it is difficult to confirm with one model, as

drug release from calcium alginate micropellets is quite complex demonstrating various mechanisms like diffusion, relaxation and erosion simultaneously.

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