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EVALUATION OF TWO TECHNIQUES FOR THE PRODUCTION OF ALGINATE-BASED MICROCAPSULES FOR ORAL DELIVERY OF IBUPROFEN

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ABSTRACT

A widely used approach for the microencapsulation of drugs especially for controlled drug delivery is emulsion polymerization. The purpose of this study was to comparatively evaluate chitosan-alginate microcapsules for oral delivery of ibuprofen using two techniques. Alginate-based microcapsules were prepared using the emulsion/internal gelation and electrostatic droplet generator/counter-ion coacervation methods. The effect of production parameters on the size of the microcapsules and *in vitro* ibuprofen release at pH 1.2 and 7.4 was determined. For emulsion/internal gelation method, the results showed that increase in stirring rate, volume of dispersion medium and viscosity of the coating materials did not significantly ($p > 0.05$) affect the size of the microcapsules. Microcapsules produced by the electrostatic droplets generator method had a narrower size distribution compared to the emulsion method. Drug release at pH 7.4 was considerably more than at pH 1.2, especially for uncoated microcapsules, microcapsules coated with high-viscosity (undigested) chitosan, and microcapsules prepared by the emulsion method. The encapsulation efficiencies of the two methods were similar as over 90% of ibuprofen was entrapped in each case. The two microencapsulation techniques can be applied in the microencapsulation of ibuprofen for oral delivery.

Key words: *Droplet generator; emulsion method; Ibuprofen; microcapsules; oral delivery*

INTRODUCTION

Generally, optimization of drug delivery seeks to achieve common goals which include:

- Drug stability over a long period of time and under a wide range of environmental conditions such as temperature, light and humidity[1].
- Convenience in administration in order to facilitate compliance[2].
- Release of the specified amount of drug at a pre-determined rate and region of drug absorption[3].

Usually, the approach is to explore the best combination of parameters and processes involved in drug production in order to achieve these goals[4]

Ibuprofen is a non-steroidal anti-inflammatory drug whose major side effect is gastro-intestinal irritation. A way to reduce this effect is to encapsulate the drug which will shield the stomach directly from it following oral administration[5]. Furthermore, microencapsulation of ibuprofen could also be used to achieve controlled release of the drug thereby reducing its frequency of administration and hence improves drug compliance.

A number of techniques are available for the microencapsulation of drugs. The counter-ion coacervation method using an electrostatic droplet generator[6] and the emulsion/internal gelation method[7] are two approaches for producing microcapsules which are potentially less hazardous. Both techniques have been described for immobilizing labile materials within alginate microcapsules [6, 8]. Previous studies reveal that microcapsules produced by the emulsion technique had a wide size range. The shape and size of the microcapsules were influenced by factors such as stirring rate, emulgent and volume of the dispersion medium. This method however, has been found suitable for large-scale microcapsule production. On the other hand, microcapsules produced by the droplet generator had a narrow size distribution and the shape and sizes were influenced by the magnitude of the applied voltage, alginate concentration and needle size. The influence of these methods of microcapsule production on the properties of the dosage forms has not been compared[6].

Chitosan and alginate are natural biodegradable polymers that have been used as excellent carriers in controlled release formulations[9]. This study, therefore, sought to investigate the effect of some production parameters on selected properties of chitosan-alginate microcapsules containing ibuprofen produced using the counter-ion coacervation and emulsion/internal gelation techniques.

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MATERIALS AND METHODS

Materials

Sodium alginate (Laboratory Burgoyne Reagents, India) and chitosan (high viscosity grade, '13,000 cps' Vansom Chemical Co, Redmond, WA) were the polymers used for microcapsule production. Ibuprofen (drug) was a gift from Fidson Healthcare Ltd, Lagos, Nigeria. Calcium chloride dihydrate (May and Baker, UK); hydrochloric acid and sodium hydroxide pellets (Fluke AG, Chemiche Fabric CH – 9470, Buch); liquid paraffin (a gift from Nomagbon Pharmacy, Benin City, Nigeria); Span 80, Tween 80 and acetic acid (Sigma-Aldrich GmbH, CH-9471 Buchs); and calcium carbonate (BDH, Poole, UK) were all of reagent grade.

Methods

Preparation of encapsulation solutions

Chitosan solution (0.1%$^{w}/_{v}$) was prepared as previously described[4] by dissolving 1g of chitosan in 500ml of distilled water containing 10ml of glacial acetic acid with the aid of a magnetic stirrer. The viscosity of the chitosan solution was reduced by digesting overnight with 2.14ml of 1% w/v sodium nitrite solution. This was followed by the dissolution of 20g of calcium chloride dihydrate and polysorbate (Tween) 80 (0.2ml) in the chitosan solution. The pH of the solution was then adjusted to 5.5 using sodium hydroxide after which it was filtered and its volume made up to 1000ml with distilled water. Another batch of chitosan solution was similarly prepared except that it was not digested with sodium nitrite.

Sodium alginate (2g) was dissolved in 50ml of distilled water to which 1g of ibuprofen was added and stirred using a magnetic stirrer until it dissolved. The volume was then made up to 100ml with more water.

Electrostatic Droplet Generation (Counter-ion coacervation) method

The electrostatic droplet generator consisted of a high voltage power supply unit (Series 230, Bertan Associates, Inc. USA) with positive and ground terminals. The system also incorporated a syringe pump (Cole-parmer Instrument Company) and a disposable syringe fitted with a flat-tipped stainless steel needle. To produce the dosage form, the solution of drug and sodium alginate is extruded from the syringe into calcium chloride solution for microspheres production or chitosan/calcium chloride solution for microcapsule production. The positive and ground terminals of the voltage power supply unit were clipped to the syringe needle and chitosan or calcium chloride solution, respectively[6].

Microcapsule production

Spherical droplets of alginate solution were formed with the syringe pump on which was fitted with a 22-guage flat-tipped needle (Chromatographic Specialties, Ontario, Canada) and extruded across a distance of 5cm, perpendicularly into the chitosan solution (50ml) contained in a glass Petri dish. An electrical field was created along the extrusion pathway[4] with the aid of the voltage power supply facility set to generate a current of 0.4mA and a variable voltage of 0 - 30kV. The syringe pump was set at an extrusion rate of 0.5ml/min. the voltage used for microcapsule production was 0, 4, and 6 kV. The droplets were pulled off and broken into fine droplets by the action of electrostatic forces before falling into the chitosan solution. The microcapsules were left for 2 min in the chitosan solution after the extrusion process and then washed, first with water and thereafter with propanol, and finally air-dried for 24 hours.

Emulsification/Internal gelation method

The method of Poncelet[7, 8] was employed. Sodium alginate (2g) was dissolved in 50ml of distilled water using a magnetic stirrer. The solution was left for 1 h to de-aerate. The pH of the sodium alginate solution was adjusted to 7.5 – 8.0 and 1g of ibuprofen was dissolved in it. The volume of the solution was then made up to 100 ml with water.

One millilitre of 20% calcium carbonate (produced by dissolving 2g of $CaCO_3$ in 100ml of water) was added to 20ml of 2% sodium alginate (with drug) solution in a beaker. A mixture of liquid paraffin (80ml) and Span 80 (1ml) was also added into the solution and stirred at 500rpm for 15 min on a magnetic stirrer to achieve homogeneity. With continued agitation, liquid paraffin (20ml) containing 1ml of glacial acetic acid was added to the solution, resulting in the liberation of Ca^{++} from $CaCO_3$ to gelate with the alginate polyanions. After 5 minutes, the oil-bead suspension was added with gentle mixing to 150ml of a 0.5% calcium chloride solution (obtained by dissolving 5g of calcium chloride in 1000ml of distilled water). Following the complete partitioning of the resulting microcapsules to the aqueous phase, the oil phase was decanted, the microcapsules were filtered on a 30µm sieve, washed with 1% Tween 80 solution and then air-dried. The procedure was repeated but with varying parameters (Table 1).

Table 1: *Parameters varied in the emulsion method*

Coating type	Alginate content (%)	Stirring rate (rpm)	Liquid paraffin (ml)	Span 80	Acetic acid (ml)
Digested Chitosan	2	500	80	Present	1
Undigested Chitosan	2	500	80	Present	1
Uncoated	2	500	80	Present	1
Uncoated	2	300	80	Present	1
Uncoated	2	400	80	Present	1
Uncoated	2	500	80	Present	1
Uncoated	2	500	60	Present	1
Uncoated	2	500	70	Present	1
Uncoated	2	500	80	Present	1
Uncoated	2	500	80	Absent	1
Uncoated	2	500	80	Present	1
Uncoated	2	500	80	Present	0.5
Uncoated	2	500	80	Present	1
Uncoated	2	500	80	Present	2.0

Evaluation of microcapsule size and weight
A light microscope with a calibrated eyepiece was used to estimate the size of the particles. All particles appearing within each field of view were counted and sized. For each sample, the diameter of each particle in four representative fields of view were used in the size analysis and the mean result was calculated. Also, the weight of each microcapsule batch prepared was taken on an analytical balance in order to determine production efficiency.

Drug release studies
The *in vitro* release of ibuprofen from the microcapsules was measured in pH 1.2 and pH 7.4 media which represent the lower and upper pH of the gastrointestinal system, respectively. A dissolution apparatus (paddle method, USP type 1) set to rotate at 80 rpm and at a temperature of 37±1^{0}C was used. A quantity of the microcapsules containing 200mg of ibuprofen was transferred into 900ml of the dissolution medium. Samples were withdrawn initially at 0, 5, 10, 15 min and thereafter at 15 min intervals up to 120 min. The absorbance of the samples was measured with a UV spectrophotometer (Milton Roy Company, USA) at a $ë_{max}$ of 260 nm. Triplicate determinations were carried out. Data analysis was carried out using instat software (Graphpad InStat tm V2.05a) and the level of significance was reported at 95% confidence interval.

Entrapment efficacy
Assay of the microcapsules for initial drug content was carried out by first soaking approximately 50mg of the microcapsules in 20ml of **0.5 M** sodium citrate solution in a scintillation vial and kept overnight (citration breaks down the gel structure that contains the entrapped drug[9]). The mixture was transferred to a mortar and crushed thoroughly with a pestle to effect maximum drug release into solution[6]. The content of ibuprofen was determined spectrophotometrically at a wavelength of 260 nm.

RESULTS AND DISCUSSION
Microcapsule size and encapsulation efficiency
Microcapsules produced with the electrostatic droplet generator (counter-ion coacervation method) appeared more uniform with a narrower size distribution than those obtained with the emulsion method (Table 2). Microcapsule size decreased as the applied voltage was increased as shown in Table 2. Other parameters that have been varied using this method in previous studies include extrusion rate and distance and they have been reported not to significantly influence microcapsule size[6]. For the emulsion method, as stirring rate was increased, microcapsule size decreased, but, the difference was not statistically significant ($p > 0.05$). However, because the dispersion medium was oily, the microcapsules tended to clump together. Microcapsules produced at 400 rpm showed a lower tendency to clump together and were more free-flowing with over 90% of drug encapsulation achieved. There was also no significant difference ($p > 0.05$) between the encapsulation efficiencies of the two methods. Furthermore, there was no significant change ($p > 0.05$) in encapsulation efficiency with varying the stirring rate for microcapsules produced using the emulsion method.

Table 2: *Effect of production parameters on microcapsule size*

Production method	Production parameters	Mean particle size (µm)±S.D
Droplet method	Applied voltage	
	-0kV	690±4.7
	-4kV	410±2.9
	-6kV	100±9.7
Emulsion Method	Stirring rate (rpm)	
	- 300	135±18.3
	- 400	129±19.8
	- 500	124±12.5
	Coating material	
	-High viscosity chitosan (undigested)	134±11.4
	- Low viscosity chitosan (digested)	130±10.8
	- Uncoated	128±19.8
	Volume of external phase (ml)	
	- 60	132±19.6
	- 70	129±18.3
	- 80	126±11.4
	Emulgent	
	- No emulgent	135±18.9
	- Span 80	128±15.3
	Volume of acetic acid (ml)	
	- 0.5	125±10.3
	- 1.0	127±18.6
	- 2.0	133±11.3

In vitro release from microcapsules
The *in vitro* release data indicate that after 2 h in pH 1.2 release medium, microcapsules produced by both methods exhibited largely identical release characteristics ($p>0.05$) for ibuprofen (see Fig. 1(a)). However, at pH 7.4, the microcapsules produced by emulsion method released 99% of its drug content compared to 18% drug release for microcapsules produced by the electrostatic droplet generator method (Fig 1(b)). This may be attributed to the fact that the latter microcapsules were coated with chitosan unlike the former which were uncoated especially since chitosan is insoluble at near neutral to alkaline pH but soluble at acid pH. Furthermore, it is likely that the applied electrical field in the droplet generator method promoted a stronger electrostatic interaction between the chitosan and alginate thereby facilitating the formation of a more compact chitosan-alginate interface which would create some resistance to diffusion by both the leaching fluid and the drug.

Effect of encapsulation parameters
Digesting chitosan overnight with sodium nitrite reduces its viscosity and this has previously been reported to influence drug release[9]. The microcapsules were coated using digested and undigested chitosan; uncoated microcapsules served as control to determine the influence of chitosan coat on the release profile. At the end of 2 h, the microcapsules coated with digested (low-viscosity) chitosan were more effective in hindering ibuprofen release than those coated with undigested (high-viscosity) chitosan. This was probably due to the capacity of the former, being less viscous, to spread, penetrate and therefore interact more effectively with

(a)

(b)

Fig 1: In vitro release of ibuprofen at pH 1.2 (a) and 7.4 (b) from microcapsules prepared using electrostatic droplet generator (□) and emulsion/internal gellation (□) methods.

the alginate core to form a more compact chitosan-alginate interface that acts as a barrier to diffusion. Unexpectedly, however, the drug release from the uncoated microcapsules was similar to that from the microcapsules coated with low-viscosity. No explanation can be proffered for this anomalous result. A similar trend was observed at pH 7.4 (Fig 2). Expectedly, the uncoated microspheres released practically all the encapsulated drug. Chitosan coated microcapsules have been shown to be more impermeable than uncoated microcapsules[10].

The volume of external phase was varied from 60 to 80% of the total volume in the emulsion method. On the in vitro release profile, the result showed that the volume of oily phase did not have any significant effect ($p>0.05$) on ibuprofen release at pH 1.2 and pH 7.4 (data not shown). Span 80 was used as a w/o emulgent while acetic acid was used as a gelling agent. Increase in the volume of the acetic acid used increased the size of the microcapsules. The presence of Span 80 exerted a slight reduction in drug release at pH 1.2

(a)

(b)

Fig 2: In vitro release of ibuprofen from microcapsules coated with undigested chitosan (□), digested chitosan (□) and from uncoated microcapsules (x) at pH 1.2 (a) and 7.4 (b).

compared with control microcapsules (without acetic acid and Span 80) but a pronounced decrease in drug release was observed when acetic acid (a gelling agent) was also included. The results at pH 7.4 followed largely the same trend (Fig 3). The influence of acetic acid is likely to be due to its gelling effect which rendered the alginate matrix more compact and, therefore, less permeable to the leaching fluid and the drug.

CONCLUSION

The findings from this work demonstrate the feasibility and potential of the electrostatic droplet generator and the emulsion methods for the production of alginate-based ibuprofen microcapsules. The techniques appear to be chemically less hazardous than the interfacial polymerization method often employed by some workers. In particular, the emulsion method seems to be suited to large-scale microcapsule production. Suitably formulated ibuprofen microcapsules manifested slower release at gastric pH thus

demonstrating a potential to provide enteric release. In addition to the alginate-based system used in this study, other appropriate polymer systems may also be adaptable for encapsulation with the techniques used in this study.

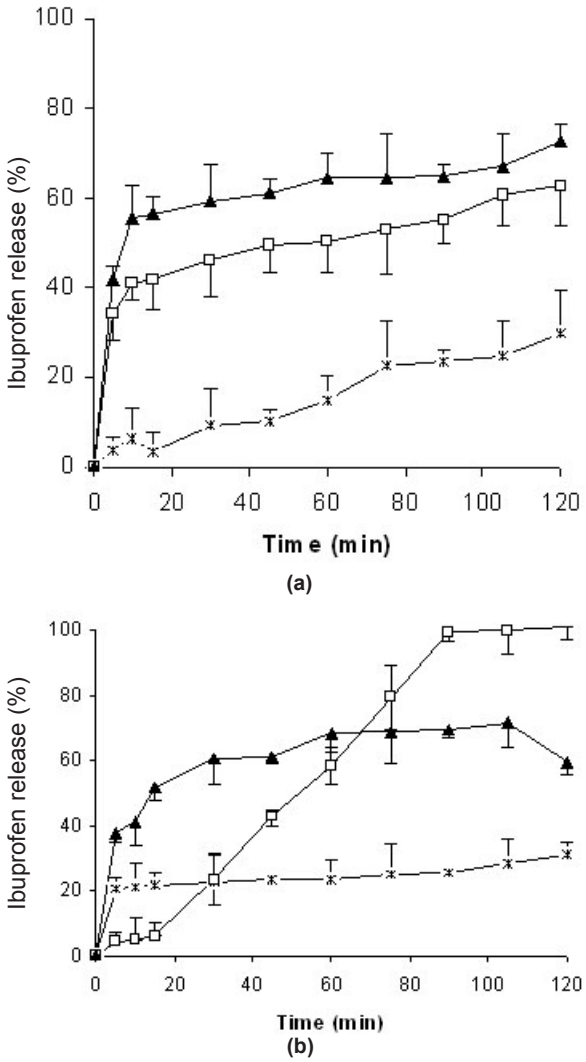

Fig 3: *In vitro release of ibuprofen from microcapsule containing emulgent (Span 80, □), (Span 80 + acetic acid,* x*) and without Span 80 (▲) at pH 1.2 (a) and 7.4 (b)*

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