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DEVELOPMENT AND EVALUATION OF IBUPROFEN-CALCIUM ALGINATE BEADS

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ABSTRACT

THE objective of this study was to develop a sustained release dosage form of Ibuprofen (IBP) using a natural polymeric carrier prepared in a completely aqueous environment. IBP was entrapped in calcium alginate bead prepared with sodium alginate by ionotropic gelation method using calcium chloride as a crosslinking agent. The drug was incorporated either into preformed calcium alginate gel beads (sequential method) or incorporated simultaneously during the gelation stage (simultaneous method). The beads were evaluated for particle size and surface morphology using optical microscopy and SEM respectively. Beads produced by the sequential method had higher drug entrapment. Drug entrapment in the sequential method increases with increase in $CaCl_2$ and polymer concentration but decreased with increase in drug concentration. And in the simultaneous method drug entrapment increases when polymer and drug concentration were increased and it increased to a certain extent with increase in $CaCl_2$ concentration and further increase resulted in lower drug loading. FTIR studies revealed that there is no interaction between drug and $CaCl_2$. XRD studies show that crystalline drug changed to amorphous state after formulation. Release characteristics of the IBP loaded calcium alginate beads were studied in enzyme free simulated gastric and intestinal fluid.

Key words: Sodium Alginate, Calcium alginate bead, Ibuprofen, ionotropic gelation.

INTRODUCTION

Among the most abundant natural polymers, polysaccharides are widely used in pharmaceutical dosage forms as excipients like suspending agents, emulsifying agents, tablet binders, gelling agents. With the advent of macromolecular chemistry, the use of polysaccharides has been extended towards new applications in pharmaceutical, biomedical, and agricultural fields.

Sodium alginate, a hydrophilic biopolymer obtained from brown seaweeds has been found to be highly promising with respect to drug delivery because of its high biological safety [1]. Chemically, it is a polysaccharide composed of varying proportion of D-mannuronic acid (M) and L-guluronic acid (G) residues which are arranged in MM or GG blocks interspersed with MG blocks[2]. In addition to its use as a thickening, gel forming and colloidal stabilizing agent in food and beverage industries, it as also used as binder in tablet formulation [3]. Its unique property of forming water insoluble calcium alginate gel through ionotropic gelation with Ca^{+2} ions in simple and mild conditions has made possible to encapsulate both macromolecular agents [4-6] and low molecular weight therapeutic agents[7-9]. The current uses of alginate based devices are mainly related to encapsulation of various classes of therapeutic agents.

In this study, IBP was incorporated into calcium alginate beads by sequential and simultaneous methods. The effect of polymer and $CaCl_2$ concentration and that of IBP concentration on drug entrapment (drug loading) and drug release characteristics were studied. The drug-loaded beads were also characterized using different techniques.

MATERIALS AND METHODS

Ibuprofen (Indian Pharmacopoeia) (M/S Albert David Pvt. Limited, Kolkata, India.), Sodium alginate (Fluka) 90 cps (1% w/v solution in water at 25ºC), Calcium chloride dihydrate (E. Merck, India). All other reagents were of analytical grade.

Preparation of beads

For bead formation, 50ml of a 2-2.5% w/v aqueous solution of sodium alginate was introduced dropwise from a glass syringe with a size-22 needle into 100 ml of an aqueous calcium chloride solution being stirred at 400 rpm. The concentration of $CaCl_2$ in the solution ranged from 1 % w/v to 3% w/v. The stirring was continued for one hour and the calcium alginate beads were harvested by filtration, washed with distilled water, and dried overnight in air.

Drug loading was carried out by two methods, designated as sequential method and simultaneous method. In the sequential method, calcium alginate beads were prepared as described in the previous paragraph. The wet beads were then immersed and stirred for 1hr in a solution containing IBP (concentration ranging from 2-3 % w/v), filtered and washed with distilled water. IBP loaded calcium alginate beads were obtained by subsequent drying. In the simultaneous method, the gelation of beads by calcium ions occurred simultaneously with the drug loading into the beads. The sodium alginate solution was introduced dropwise into $CaCl_2$ solutions (concentration ranging from 1-3 %w/v) which also contained IBP (concentration ranging from 2-3% w/v). After 1hr of interaction, the beads were removed from the counter ion solution. The drug loaded beads were washed and dried in a manner similar to that of blank beads (beads without drug).

Drug entrapment efficiency

Alginate beads (20 mg) were accurately weighed in an electronic balance (Precisa XB 600 MC, Precisa Instrument Ltd; Switzerland), immersed in 250 ml USP phosphate buffer (PB) solution (PH-6.8), and shaken for 2h on a mechanical shaker. The beads were crushed and further shaken for 1h. The solution was filtered and an aliquot following suitable dilution was analyzed at 222 nm in a UV-Visible spectrophotometer (model Cary-50 Bio-spectrophotometer, VARIAN, Australia)) and the content of the beads was determined using a calibration curve constructed using PB solution of PH 6.8. The reliability of the above analytical method was judged by conducting recovery analysis at three levels of spiked drug solution in the presence or absence of the polymers for three consecutive days. The recovery averaged 98.45±2.68 %. DEE was determined using the following relation:

DEE (%) = (Determined drug content / Theoretical drug content) x 100

Particle size distribution

The particle size determination of IBP loaded calcium alginate beads were carried out using an optical microscope along with a stage micrometer having an accuracy of 0.01mm. A suspension of beads in liquid paraffin was prepared in a beaker and then one drop of the same was dropped on a clean glass slide and covered with a cover slip. The average sizes of 100 beads were determined for each formulation using the calibration factor. The average diameter of the beads was calculated using the following formula : $X = \frac{\sum(X_i)}{N}$

X = average particle diameter, X_i = Individual diameter of beads, N = Number of beads

Scanning Electron Microscopy

The surface morphology of drug loaded beads obtained from various percentages of polymer, $CaCl_2$ and drug were studied by using a scanning electron microscope (model JEOL JSM-6360, Japan). The beads were mounted on an appropriate stub and then coated with carbon and gold (100 and 50Å thickness respectively) sputter module in a vacuum evaporator in an argon atmosphere. The coated samples were then observed under scanning electron microscope operated at 15KV.

Furrier Transformed Infra Red analysis

The IR analysis of pure drug, polymer, and drug loaded beads prepared by both the methods were analyzed with FTIR spectrophotometer (Shimadzu FTIR-8400, Japan). All the samples were crushed with potassium bromide to get pellets at 600kg cm^{-2}. Spectral scanning was done in the range of 400-4000 cm^{-1}.

X-ray Diffraction study

To understand the crystalline state of the drug in the polymer matrix, the X-ray diffraction pattern of drug loaded beads was performed and compared with that of pure drug. Powder forms of the samples were exposed to Cu radiation (30kv □ 15mA) in a wide-angle X-ray diffractometer (Miniflex gonio Meter, Japan). The instrument was operated in continuous mode in increments of 1º/min and scanned over a 2O range of 10 to 90^0

In vitro drug release study

In-vitro drug release study was carried out in acidic solution 0.1(N) HCl (PH-1.2) and in USP PB solution (PH 6.8) using USP-II dissolution rate test apparatus (model TDP-06P Electro Lab, Mumbai, India). 20 mg beads were placed in 500 ml acidic solution or 500 ml PB solution (37±1ºC) and rotated with paddle at 75 rpm. Aliquot was withdrawn at different times and replenished immediately with the same volume of fresh solution. Undiluted or suitably diluted withdrawn samples were analyzed spectrophotometrically at 220 nm for acidic solution and 222 nm for PB solution. The amount of drug released in acidic solution and PB solution were calculated from the calibration curves drawn respectively, in 0.1(N) HCl and PB solution (PH 6.8). Each release study was conducted four times.

RESULTS AND DISCUSSION

In this investigation, a simple and inexpensive method was developed for the preparation of calcium alginate beads. Crosslinking of sodium alginate was done using $CaCl_2$ and IBP was loaded in the same. Various compositions of the formulation variables were used for the present study are given in table 1.

Table 1: Composition of IBP loaded calcium alginate beads prepared by sequential and simultaneous method.

Formulation code	Formulation variables		
	Conc. of $CaCl_2$ (% w/v)	Conc. of sodium alginate (%w/v)	Drug (% w/v)
A1	1	2	2
A2	1	2	3
A3	1	2.5	2
A4	1	2.5	3
B1	2	2	2
B2	2	2	3
B3	2	2.5	2
B4	2	2.5	3
C1	3	2	2
C2	3	2	3
C3	3	2.5	2
C4	3	2.5	3

Particle size was in the range of 1005 µm to 1075 µm for the beads obtained using the sequential method and 1057 µm to 1207 µm for those from the simultaneous method(table 2). The particle size of the beads prepared by the simultaneous method decreases with increased in $CaCl_2$ concentration.

Table 2: Effect of sodium alginate, $CaCl_2$, and IBP concentration on particle size, and drug loading.

Formulation code	Mean particle size (µm±sd, n=3)	Drug loading (% ±sd , n=3)
Sequential method		
A3	1065±0.01	53.22±0.02
B3	1060±0.01	58.15±0.01
C2	1057±0.01	45.21±0.02
C3	1005±0.25	62.15±0.01
C4	1075±0.01	56.28±0.05
Simultaneous method		
A4	1207±0.50	46.89±0.01
B2	1158±0.75	52.02±0.03
B3	1151±0.25	55.32±0.01
B4	1106±0.25	58.28±0.02
C4	1057±0.50	55.60±0.03

Scanning Electron Microscopy

The surface morphology of the prepared beads was studied by scanning electron microscopy (SEM) and the SEM photographs are given in Fig. 1.

SEM photographs of the blank beads when compared with drug loaded beads show difference in surface morphology for both the sequential and simultaneous method. Smoothness increase when drug was loaded in the beads.

The SEM photographs of the drug loaded beads (Fig. 1[A]) show that the drug is dispersed in the polymeric matrix without having any coat, which further confirms that this system is a polymeric matrix system for beads prepared by both sequential and simultaneous methods.

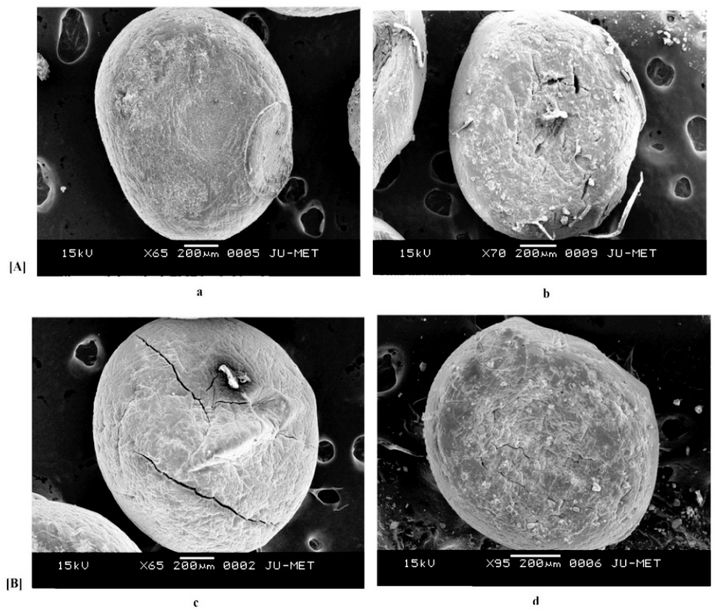


Figure 1: [A] SEM photographs of IBP loaded calcium alginate beads prepared by sequential method (a) Drug loaded bead (b) After dissolution

[B] SEM photographs of IBP loaded calcium alginate beads prepared by simultaneous method (c) Drug loaded bead (d) after dissolution

The SEM photographs presented in the Fig. 1[B] also show difference in surface morphology of the prepared beads before and after the completion of *in-vitro* dissolution study for both the sequential and simultaneous methods. The surface of beads after dissolution was rougher than before dissolution.

Drug loading

Drug loading was found to be in the range of 42-62% for beads prepared by the sequential method and 39-58% for the simultaneous method. Drug loading was found to be directly proportional to polymer concentration [10] in both the methods. But the effect of crosslinking agent and drug concentration on drug loading was different in both methods.

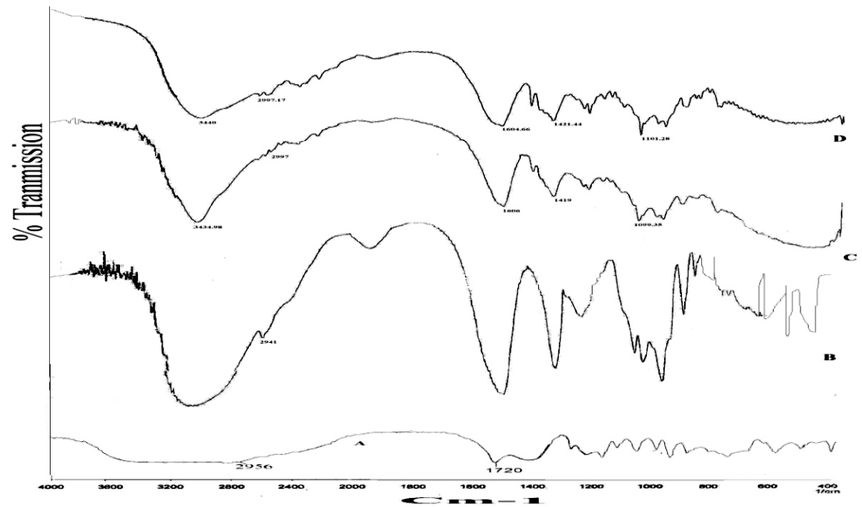
Higher loading efficiency was obtained as the concentration of alginate increased. This may be attributed to the greater availability of active calcium binding sites in the polymeric chains and consequently, the greater degree of crosslinking as the quantity of sodium alginate increased [11]. For the sequential method, batch C3 had the highest drug loading (62%) and the use of drug concentrations greater than 2% w/v did not result in further enhancement of drug loading.

It was observed that the efficiency of loading IBP into the calcium alginate beads by the simultaneous method was lower than by the sequential method [12]. For the simultaneous method, batch B4 had the highest drug loading (58%). When the drug loading was carried out by the simultaneously with the gelation of alginate by Ca^{+2}, the counterion solution contained both the drug molecule and $CaCl_2$. The drug molecules and Ca^{+2} ions diffuse in the same direction, from the solution into the sodium alginate solution and competed simultaneously for common binding sites along the alginate chains. The amount of associated Ca^{+2} ions (and the drug molecules) in the beads was a function of the concentration ratio of $CaCl_2$: IBP in the solution.

Increase in $CaCl_2$ concentration from 1 to 3%, polymer concentration from 2 to 2.5% and drug concentration from 2 to 3% resulted in a corresponding increase in the drug entrapment from the 53% to 62%, from 45% to 62% and decrease from 62% to 42% respectively for the sequential method. Similarly in the simultaneous method increase in drug entrapment from 47% to 58%, from 52% to 58% and from 55% to 58% respectively was observed.

Furrier Transformed Infra Red analysis

FTIR spectral data were used to confirm the chemical stability of Ibuprofen in alginate beads. FTIR spectra of pure drug, sodium alginate, IBP loaded calcium alginate beads prepared by sequential and simultaneous method were compared in Fig. 2. The characteristics bands corresponding to C=O stretching and –OH stretching of IBP appeared in FTIR spectrum respectively at 1720 cm^{-1} and 2956 cm^{-1}. The spectra obtained from drug loaded beads prepared by both the methods, indicate the presence of the characteristics bands of the drug at almost the same wave number.



IBP loaded beads prepared by simultaneous method(D)

X-ray Diffraction study

In order to confirm the physical state of the drug in the beads, data for the X-ray diffraction studies of the pure drug, polymer, empty beads and beads containing the drug carried out is shown in Fig. 3. No characteristic XRD pattern was observed in the case of drug loaded beads. Thus from the X-ray diffraction data of the drug loaded beads, it can be inferred that the drug was not present in the crystalline state in the bead matrix. It was in the amorphous state. This clearly indicated that changes in the crystalline state of the drug occurred during the preparation of the beads by this ionotropic gelation method.

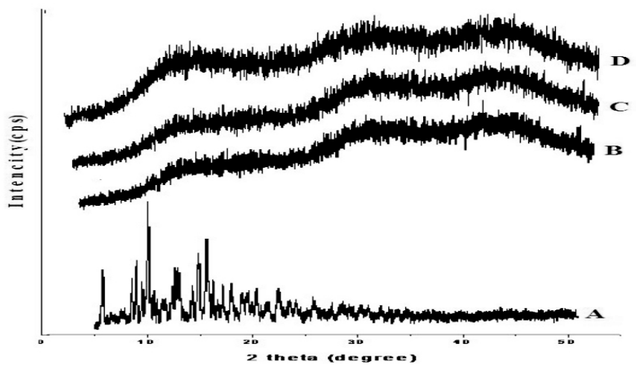


Figure 3 : X ray diffractogram of IBP (A), Sodium alginate (B), IBP loaded beads prepared by sequential method(C), IBP loaded beads prepared by simultaneous method(D)

In-vitro drug release

The release profile of IBP in enzyme free simulated gastric fluid (SGF) followed by enzyme free simulated intestinal fluid (SIF) from the calcium alginate beads prepared under different conditions have been represented in Fig. 4-6. The drug release from the alginate beads depends on the penetration of the dissolution medium into the beads, the eventual swelling and dissolution of alginate matrix and the dissolution of the drug subsequent to leaching through the swollen matrix. In SGF alginate beads prepared by the sequential method IBP releases about 30-40 % drug in first 2h. And after that rest of the drug releases in the SIF which continues upto 9h where by it releases 82-89% of the drug. It was found that drug release is accompanied by a burst release which may be due to the highly water soluble nature of the drug.

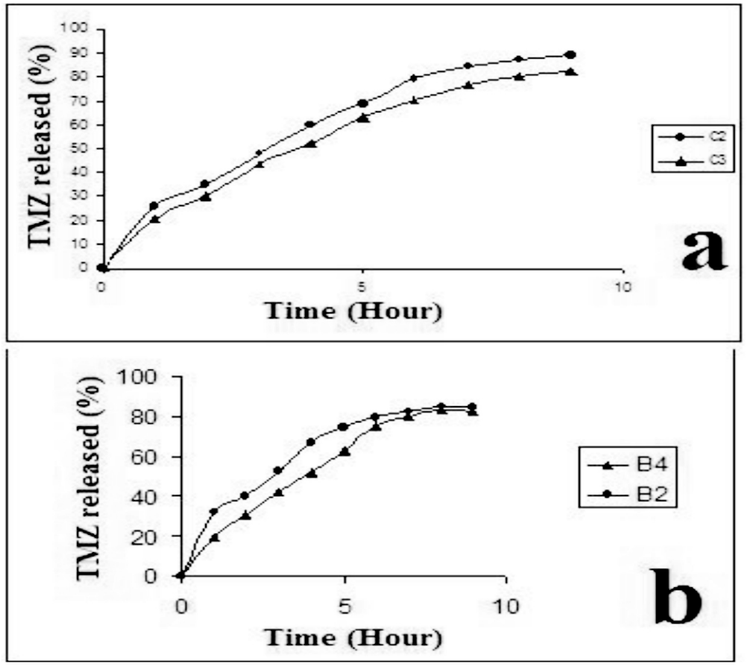


Figure 4 : Effect of sodium alginate concentration on IBP release from calcium alginate beads (a) sequential method (b) simultaneous method. (Maximum SEM ±3.70%, n= 4).

i. Effect of polymer

To study the effect of sodium alginate concentration on IBP release, two different concentrations, 2 and 2.5% w/v were used. Fig. 4 shows the influence of the concentration of sodium alginate solution on Ibuprofen release behavior from calcium alginate loaded beads prepared by sequential and simultaneous method. Lower concentrations of sodium alginate led to faster drug release, with 89.05±0.178% of drug release within 9h in sequential method. Increase in alginate concentration decreases the release rate. Thus the results indicate that drug release was directly proportional to sodium alginate concentration [11, 13]. The principal gelation or cross-linking of sodium alginate with $CaCl_2$ is based on the tight junction between the guluronic acid residues [14]. The number of the apparent cross-linking points formed within increases with increasing alginate concentration in the formulation. This can be correlated with the particle size studies where as the alginate concentration increased the particle size decreased due to the formation of more rigid and compact matrix, consequently retarding the IBP release.

In the case of IBP loaded calcium alginate beads prepared by simultaneous method similar behavior was also observed.

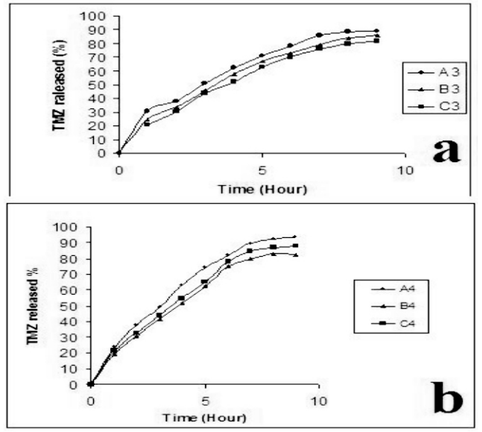


Figure 5 : Effect of $CaCl_2$ concentration on IBP release from calcium alginate beads (a) sequential method (b) simultaneous method. (Maximum SEM ±2.50%, n= 4).

ii. Effect of $CaCl_2$

The release behavior of calcium alginate beads prepared by sequential method with different concentrations of $CaCl_2$ (1-3 % w/v) is indicated in fig. 5. Drug release was sustained from 38 % to 30 % in SGF for 2h and 89 % to 82 % in SIF fluid upto 9h with increasing $CaCl_2$ concentration. Thus in the sequential method as the concentration of crosslinking agent increased, drug release decreased. Beads prepared with 3% w/v $CaCl_2$ showed the most sustained release effect due to more crosslinking resulting in the formation of a more rigid gel network and hence greater sustained release characteristics. It was confirmed by particle size studies, where the size of the beads was found to be decreased as the concentration of crosslinking agent increased [10]. It was also evident from the literature [14] that diffusion of drug from alginate matrix decreased as the concentration of $CaCl_2$ solution increased in sequential method, probably due to more number of cross-linking with sodium alginate.

In simultaneous method IBP releases was sustained from 30% to 37% in SGF for 2h and from 93% to 82% in SIF upto 9h (Fig. 5). But in case of simultaneous method 3% crosslinking agent does not show the highest sustained effect. It may be due to the low drug loading [12].

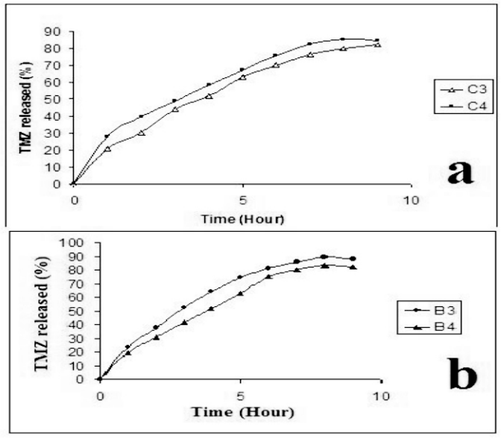


Figure 6 : Effect of IBP concentration on IBP release from calcium alginate beads (a) sequential method (b) simultaneous method. (Maximum SEM ±3.30%, n= 4).

iii. Effect of drug concentration

It was found that drug releases within the 1st hour indicative of a burst effect. This could be attributed to the highly water soluble nature of the drug. Similar result was found by Ray et al, [15] during preparation of diltiazem resin complex loaded carboxymethyl xanthan beads.

The effect of drug concentration during *in-vitro* drug release study does not affect the drug release from the calcium alginate beads. The drug concentration was varied from 2 to 3% w/v to study the effect of drug release shown in fig. 6. IBP release from beads prepared by sequential method (batch C3) which contained 2% w/v IBP shows more sustained effect with drug loading of about 62%.

But in case of simultaneous method (batch B4) which contains 3% w/v drug shows the more sustained effect with drug loading of about 58%. It was found that drug release was greatly dependent on the drug loading.

CONCLUSION

Ibuprofen was entrapped in calcium alginate bead prepared with sodium alginate by ionotropic gelation method using calcium chloride as a crosslinking agent. The drug was incorporated by two methods, sequential and simultaneous method. Beads produced by the former method had higher drug entrapment. The beads were evaluated for drug entrapment, particle size and release characteristics in enzyme free simulated gastric and simulated intestinal fluid. The drug entrapment in sequential method increases with increased $CaCl_2$ and polymer concentration but it decreased with increased drug concentration. And in simultaneous method drug entrapment increases with polymer and drug concentration increased and it increased to a certain extent with increase in the concentration of $CaCl_2$ and after further increase it decreased. Drug release was directly proportional to the polymer concentration for the drug loaded beads prepared by both the methods. Increase in $CaCl_2$ concentration retarded the drug release in sequential method and for the simultaneous method the retardation in drug release is upto a certain concentration of $CaCl_2$. The drug concentration exhibits a drug loading dependent effect on the release behavior in both the methods.

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ANALYTICAL PLATFORMS USED IN THE FIELD OF METABONOMICS : A MINI REVIEW

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Running title: Analytical platforms used in Metabonomics

ABSTRACT

Metabonomics involves metabolic profiling of various biomatrices in response to any diseased condition or genetic modification or due to effect of environment or lifestyle related factors With its advent, the field of metabonomics has made valuable contributions and insight to system biology research. Metabonomics provides a powerful tool complementary to genomics and proteomics and can be used to obtain valuable information into functional biology, toxicology, pharmacology and diagnosis of diseases. This mini-review briefly describes the advantages, disadvantage and applications of the various analytical platforms used in metabonomics such as nuclear magnetic resonance (NMR) spectroscopy, Fourier transform infrared (FTIR) spectroscopy, LC with ultraviolet or coulometric detection, capillary electrophoresis (CE) with ultraviolet detection and mass spectrometry (MS) based techniques like direct infusion MS, gas chromatography mass spectrometry (GC/MS), liquid chromatography mass spectrometry (LC/MS) or capillary electrophoresis mass spectrometry (CE/MS).

Keywords: metabonomics, analytical techniques, NMR, GC/MS, LC/MS

INTRODUCTION

Since its inception the field of metabonomics has grown remarkably in terms of its applications and contributions to system biology research. Metabonomics provides a powerful tool for gaining valuable insight into functional biology, toxicology, pharmacology and diagnosis of diseases. Metabonomics involves determination of changes in metabolic profiles of living organisms in response to any diseased condition or genetic modification or due to effect of environment or lifestyle related factors [1]. Metabonomics is complementary to genomics and proteomics as it measures the perturbed metabolic end-points due to environmental, pharmacological or pathological influences while in genomics and proteomics, more upstream biological events are typically profiled and studied [2]. It involves the analysis of various biological matrices such as plasma, urine and tissues using suitable analytical platforms. Metabonomics can be carried out with a global non-targeted approach as well as with a targeted approach. In targeted metabonomics, alterations in the levels of a specific class of metabolites or metabolites belonging to a specific metabolic pathway are ascertained using an appropriate analytical technique [3]. In global non-targeted metabonomics, metabolites belonging to diverse metabolic pathways are profiled. The metabolites that are determined in non- targeted approach belong to various chemical classes such as organic acids, amino acids, fatty acids, amines, sugars, sugar alcohols, steroids, nucleic acid bases and other miscellaneous substances. So, multiple complementary analytical techniques are often utilized for non-targeted metabonomics of biological matrices, in order to cover as much of metabolic space as possible [4]. In this mini-review, the different analytical platforms used in metabonomics as well as their advantages, disadvantage and applications have been described in a succinct manner.