

## A Study of *in Vitro* Drug Release from Zirconia Ceramics

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In the field of biomedical applications, Zirconia is an important biomaterial due to its excellent biocompatibility and high mechanical strength. Block forms of such bio inert ceramics can be used as defect bone filler. Designing such implants associated with therapeutic agents like antibiotics, anti-inflammatory etc. exhibiting targeted drug delivery with controlled release profile is a challenge. In the present work, an *in vitro* drug release of two drug loaded forms (punched pellet and alginate beads) of the zirconia and yttria stabilized zirconia is studied. The ceramics are synthesized by combustion method. The model drugs selected are the antibacterial drug, ciprofloxacin hydrochloride (CFH) and anti-inflammatory drug, diclofenac sodium (DFS).

### Introduction

Ceramics are increasingly used for biomedical applications in recent years. The ceramics that are used in implantation and clinical purposes included alumina, partially stabilized zirconia (PSZ), bio-glass, glass ceramics, calcium phosphates (HAP,  $\beta$ -TCP) and crystalline or glassy forms of carbon and its compounds [1,2].

Zirconia is a biomaterial that has advantages over other ceramics because of its high mechanical strength and fracture toughness. Yttrium Oxide partially stabilized Zirconia belongs to a new class of ceramics exhibiting an improved toughness when compared to alumina. Zirconia shows different crystal structures at different temperatures such as at 1000-1100°C it shows tetragonal structure and cubic phase at around 2000°C. Yttrium Oxide ( $Y_2O_3$ ) stabilizes the tetragonal phase, so that, upon cooling, the tetragonal crystals made of  $ZrO_2$ - $Y_2O_3$  can be maintained in meta stable state and not transforms in a monoclinic structure [3]. Today's main application of Zirconia ceramics is THR ball heads [4].

Yoshiki et al., studied the wear of Yttria stabilized Zirconia in the femoral head. [5]. The strength

and reliability of surface treated Yttria stabilized Zirconia dental ceramics has been studied by Toma Kosma et al.[6].

Though zirconia ( $ZrO_2$ ) and Yttria stabilized Zirconia ( $Y$ - $ZrO_2$ ) have wider applications such as hip and knee prostheses, hip joint heads, temporary supports, tibial plates, dental crowns, not much literature reports are available on the studies of this oxide ceramics as drug carriers. Present work aims to study the *in vitro* drug release using the above mentioned oxide bioceramics as carriers. The model drugs selected are Ciprofloxacin HCl (CFH) and Diclofenac Sodium (DFS).

### Materials And Methodology

#### Materials

Zirconyl Nitrate  $ZrO(NO_3)_2 \cdot XH_2O$  (98%, CDH Chemicals, India), Yttrium Oxide  $Y_2O_3$  (98%, CDH Chemicals, India), Urea (SD Fine Chemicals, India), Sodium Alginate (SD Fine Chemicals, India), Calcium Chloride (SD Fine Chemicals, India), Ciprofloxacin HCl and Diclofenac Sodium were obtained from Aurobindo Pharm Ltd, Hyderabad, India.

### **Instruments**

Veego USP Dissolution Apparatus, FTIR (Thermonicolet 330), XRD (Philips), High temperature muffle Furnace, UV Spectrophotometer (Schimadzu 1601), Viscotester 550, Monsanto Hardness tester.

### **Synthesis of Zirconia**

The synthesis of  $ZrO_2$  involves two steps. In the first step the precursors were prepared by self sustaining combustion technique using urea as a fuel. In the second step the precursors were heated at elevated temperatures in order to get pure crystalline materials. The procedure for synthesis of the above mentioned materials are given below. The required amount of Zirconyl Nitrate was dissolved in minimum quantity of distilled water. To the solution appropriate amount of urea was added and mixed thoroughly. The mixture was heated using an electrical Bunsen burner. The clear solution was evaporated. The voluminous mass obtained was ground well. The precursor thus obtained was heated at  $700^\circ C$  for 3hrs.

### **Synthesis of Yttria Stabilized Zirconia**

The required amount of Zirconyl Nitrate was dissolved in minimum quantity of distilled water. Specified amount of Yttrium oxide was dissolved in 1:1 Nitric acid, this solution mixed with Zirconyl nitrate solution. To the solution appropriate amount of urea was added and mixed thoroughly. The mixture was heated using an electrical Bunsen burner. The clear solution was evaporated. The voluminous mass obtained was ground well. The precursor thus obtained was heated at  $700^\circ C$  for 6hrs and  $1050^\circ C$  for 12hrs.

### **Preparation of Pellets by Punching Method**

Drug loaded implants were prepared by taking Drug and carrier at 1:2 ratio (weight ratio). A homogeneous blend was made by thorough mixing for about 10-20 minutes using pestle and mortar. To improve the compaction properties the above mixture was granulated using gelatin as a binding agent. To the mixture 3-5 drops of 5% gelatin solution were added and a paste was obtained. The paste was dried in a hot air oven at  $70^\circ C$  for 1hr. The dried mass was ground and the powder was punched into pellets (8mm diameter and 3mm thick) by applying a pressure

of  $4 \text{ Kg/cm}^2$ . The pellets obtained were used for dissolution studies.

### **Preparation of Drug Loaded Alginate Beads**

Drug loaded alginate beads were prepared by extruding a solution of sodium alginate (2.5%W/V) containing 1% drug through a syringe into a solution of calcium chloride (2.5%W/V) of known concentration. The viscosity of the drug containing sodium alginate gel was determined at room temperature. The equipment VISCOTESTER VT 550 was used. After 5 minutes of contact time, the beads were filtered and air-dried. The excess of calcium chloride adhering to the surface of the beads was removed by washing with water followed by air-drying overnight. The average bead size was measured as 2.5mm with an accuracy of around  $\pm 0.001 \text{ mm}$ . Similarly drug and ceramic loaded alginate beads were also prepared.

### **In Vitro Drug Release From Pellets**

The pellet containing the carrier and drug was placed in the basket of USP Dissolution apparatus. The in vitro release of Ciprofloxacin HCl and Diclofenac Sodium from pellets was carried out at  $37^\circ C$  in dissolution medium (deionized water) using USP Dissolution Apparatus with 900 ml of dissolution medium. The release medium was collected at regular time intervals for 8hrs and replaced with a fresh medium (2ml) each time. The amount of Ciprofloxacin and Diclofenac Sodium released was measured at  $\lambda_{\text{max}}$  of 271 and 276 nm respectively using Shimadzu UV 1601 spectrophotometer. The experiments were carried out in duplicate.

### **In Vitro Drug Release from Alginate Beads**

The drug loaded alginate beads were taken in a pouch and placed in the basket of USP Dissolution apparatus. The in vitro release of the drug Ciprofloxacin and Diclofenac Sodium from the beads was carried out at  $37^\circ C$  in dissolution medium (deionized water) using USP Dissolution Apparatus with 900 ml of dissolution medium. The release medium was collected at regular time intervals for 8hrs and replaced with a fresh medium (2ml) each time. The amount of Ciprofloxacin and Diclofenac Sodium released was measured at  $\lambda_{\text{max}}$  of 271 and 276 nm respectively using Shimadzu UV 1601 spectrophotometer. The experiments were carried out in duplicate.

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Similar experiments were carried out for drug and ceramic loaded alginate beads also.

### Characterization

The compounds were analyzed by powder X-ray diffraction (Phillips, CuK  $\alpha$ ) at room temperature for phase purity. The FT-IR spectra (Thermonicolet- 330) were recorded in the range 2000-4000  $\text{cm}^{-1}$  using KBr technique.

### Results And Discussion

#### Synthesis and Characterization of $\text{ZrO}_2$ and $\text{Y-ZrO}_2$

The Zirconia and yttria stabilized Zirconia was prepared by combustion method using urea-nitrate mixture. This method is chosen because self sustaining combustion process is rapid and leads to direct conversion from the molecular mixture of the precursor solution to the final oxide products. From the powder X-ray diffraction it is observed that the two oxide ceramics are pure and crystalline. The lattice parameters are in agreement with the reported values. In the present work zirconia as well as 4 mol % yttria stabilized zirconia crystallize in tetragonal system with the cell parameters  $a = 4.74 \text{ \AA}$ ,  $c = 12.91 \text{ \AA}$  and  $a = 5.12 \text{ \AA}$ ,  $c = 5.91 \text{ \AA}$  respectively.

#### Study of *In vitro* drug release

The ceramic implants are prepared by two methods. In one method, the drug loaded ceramic mixture is compressed into pellets using gelatin (7) as a binder. In the other method, drug loaded ceramic containing alginate (8) beads are prepared. Alginate bead method is chosen by assuming that it would provide controlled and targeted release of the drugs.

#### *In vitro* release of drugs from compacted pellets

The dissolution experiment using CFH and DFS mixed Zirconia pellets was carried out at  $37^\circ\text{C}$  in deionized water medium independently. In the case of CFH mixed ceramic pellet, nearly 65.9% of the drug was released within 30 minutes. After 60 minutes nearly 98.6% of the drug was released. Around 99% of the drug has been released at 150 minutes. After 180 minutes the pellet was completely disintegrated. The CFH release pattern from  $\text{ZrO}_2$  pellet is shown in Fig 1.

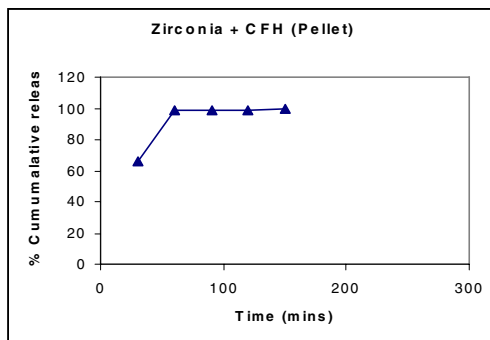


Fig 1. The CFH release pattern from Zirconia + CFH Pellet

Similarly from DFS mixed zirconia pellet, nearly 64.4% of the drug was released within 30 minutes. After 60 minutes nearly 97.9% of the drug was released. Around 99% of the drug has been released at 120 minutes. After 150 minutes the pellet was completely disintegrated. The DFS release pattern from  $\text{ZrO}_2$  pellets is shown in Fig 2.

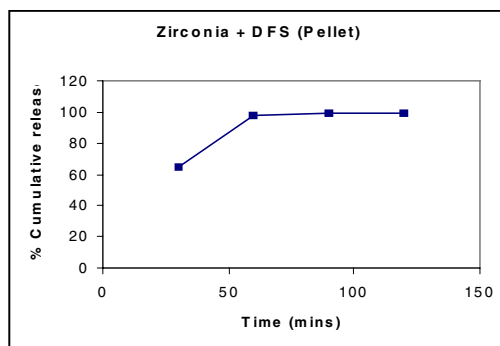
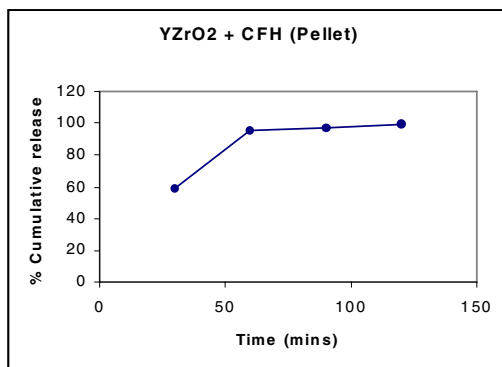


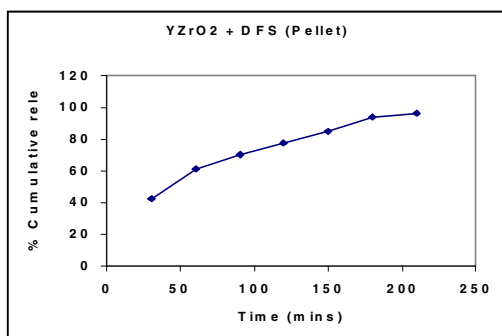
Fig 2. The DFS release pattern from Zirconia + DFS Pellet

The dissolution study of CFH added yttria stabilized zirconia pellet indicates that nearly 58.6% of the drug was released within 30 minutes. After 60 minutes nearly 95.4% of the drug was released. Around 99% of the drug has been released at 120 minutes. After 150 minutes the pellet was completely disintegrated. The CFH release pattern from  $\text{YZrO}_2$  pellet is shown in Fig 3.



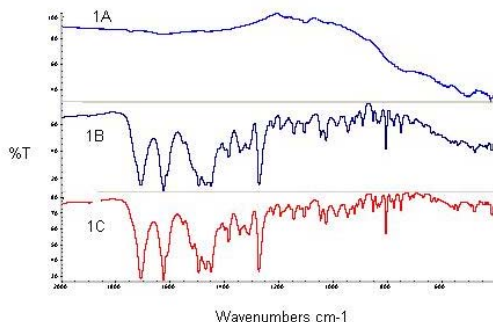
**Fig 3. The CFH release pattern from Y-ZrO<sub>2</sub> + CFH Pellet**

The DFS mixed yttria stabilized zirconia pellet showed a release of nearly 42.6% of the drug within 30 minutes. After 60 minutes nearly 60.9% of the drug was released. Around 96% of the drug has been released at 210 minutes. After 240 minutes the pellet was completely disintegrated. The DFS release pattern from YZrO<sub>2</sub> pellet is shown in Fig 4.

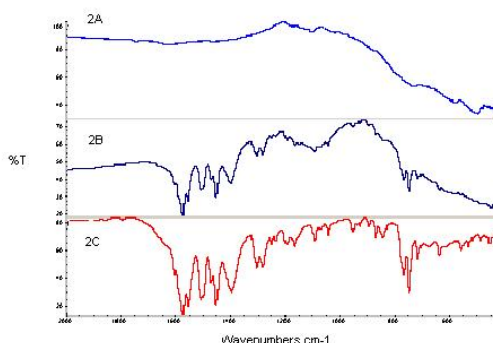


**Fig 4. The DFS release pattern from YZrO<sub>2</sub> + DFS Pellet**

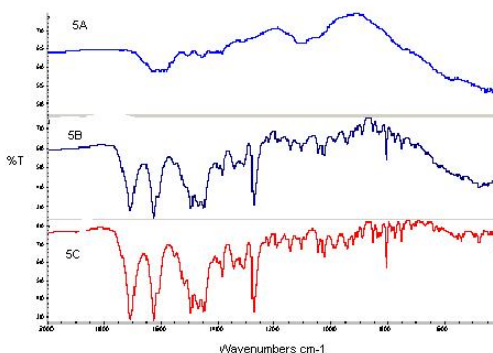
The release behavior of the drug could be influenced by the method of synthesis of the ceramic (both zirconia and yttria stabilized zirconia) which decides the particle size and by the nature of drug and ceramic binding strength. The fast release observed in the present study indicates poor binding between the drug and the ceramics. The absence of chemical interaction between the drug and the carrier is visible from FT-IR spectrum (Figs. 5-8).



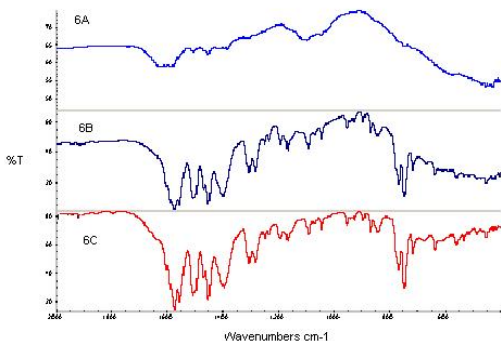
**Fig 5. IR spectrum of Zirconia + Ciprofloxacin loaded pellets(1A: Zirconia ;1B: Zirconia + Ciprofloxacin; 1C: Ciprofloxacin)**



**Fig 6 IR spectrum of Zirconia + Diclofenac sodium loaded Pellets( 2A: Zirconia ; 2B: Zirconia + Diclofenac Sodium ; 2C: Diclofenac Sodium)**



**Fig 7 - IR spectrum of Yttria stabilized zirconia + Ciprofloxacin HCl Pellets (5A: Yttria stabilized Zirconia ; 5B: Yttria stabilized Zirconia + Ciprofloxacin HCl Pellets ; 5C: Ciprofloxacin HCl)**



**Fig 8. IR spectrum of Yttria stabilized Zirconia + Diclofenac Sodium Pellets (6A: Yttria stabilized Zirconia; 6B: Yttria stabilized Zirconia + Diclofenac Sodium Pellets; 6C: Diclofenac Sodium)**

The results obtained in this study show that diluting the drug using  $ZrO_2$  (1:2 weight ratio) extends the drug release for 150 minutes in the case of both CFH and DFS. Similarly, diluting the drug using  $YzrO_2$  (1:2 weight ratio) extends the drug release for 150 minutes in the case CFH loaded pellets and for DFS loaded pellets drug release is extended for 240 minutes.

The percentage cumulative release profiles of both the drugs CFH and DFS (Figs 1, 2, 3, 4) indicate that the diffusion of the drugs from the respective compacted pellets follows the same mechanism.

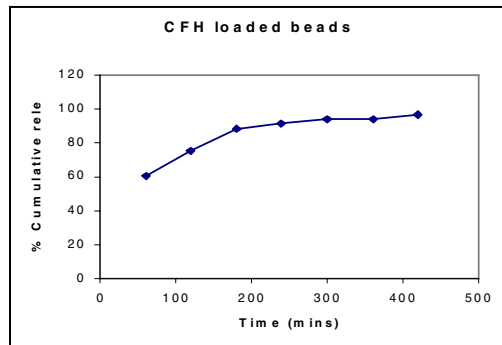
#### ***In vitro release of drugs from alginate beads***

The dissolution experiment using drug loaded alginate beads were carried out initially. The results were compared with the drug release from drug loaded ceramic containing alginate beads. Nearly 60.9% of the CFH drug was released within 60 minutes. After 180 minutes nearly 88.5% of the drug was released. Around 96% of the drug has been released at 420 minutes. The CFH release pattern from alginate beads is shown in Fig 9.

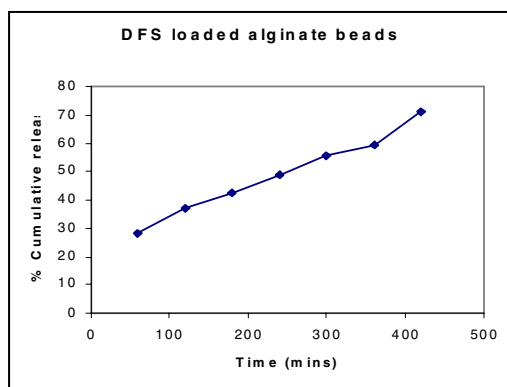
About 28.4% of the DFS drug was released within 60 minutes. After 180 minutes nearly 42.4% of the drug was released. Around 71.1% of the drug has been released at 420 minutes. The DFS release pattern from beads is shown in Fig 10.

#### ***In vitro release of drugs from ( $ZrO_2$ + drug) loaded Alginate beads***

The results obtained when the dissolution experiments were carried out using drug loaded ceramic containing alginate beads are given

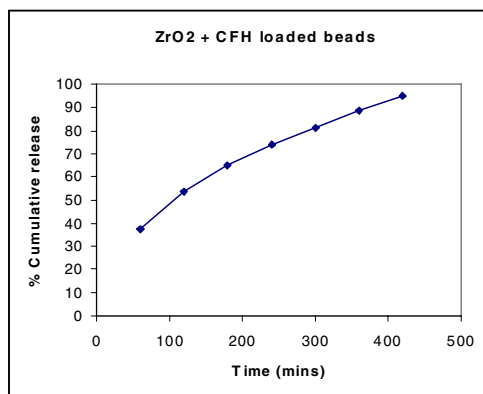


**Fig 9. The CFH release pattern from alginate beads**



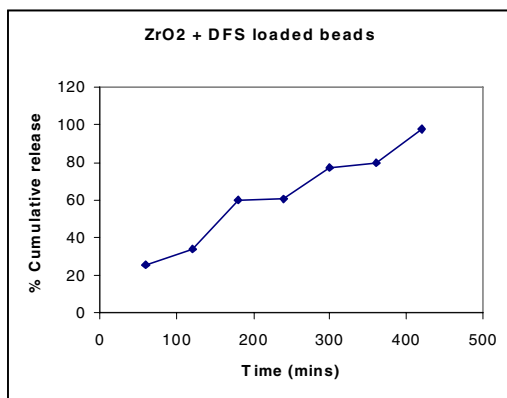
**Fig 10. The DFS release pattern from Alginate beads**

below. Nearly 37.3% of CFH drug was released within 60 minutes. After 180 minutes nearly 64.9% of the drug was released. Around 94.9% of the drug has been released at 420 minutes. The CFH release pattern from  $ZrO_2$  + CFH loaded alginate beads are shown in Fig 11.



**Fig 11. The CFH release pattern from  $ZrO_2$  + CFH loaded Alginate beads**

Nearly 25.8% of DFS drug was released within 60 minutes. After 180 minutes nearly 59.8% of the drug was released. Around 97.8% of the drug has been released at 420 minutes. The DFS release pattern from  $ZrO_2$  + DFS loaded alginate beads are shown in Fig 12.



**Fig 12. The DFS release pattern from  $ZrO_2$  + DFS loaded Alginate beads**

#### ***In vitro release of drugs from ( $YZrO_2$ + drug) loaded Alginate beads***

When drug containing yttria stabilized zirconia ceramic loaded alginate beads were subjected to dissolution experiments, nearly 62.8 % of CFH drug was released within 60 minutes. After 180 minutes nearly 85.1% of the drug was released. Around 97.4% of the drug has been released at 420 minutes. The CFH release pattern from  $YZrO_2$  + CFH loaded alginate beads are shown in Fig 13.

Similarly, about 41.7% of DFS drug was released within 60 minutes. After 180 minutes nearly 53.5% of the drug was released. Around 86.5% of the drug has been released at 420 minutes. The DFS release pattern from  $YZrO_2$  + DFS loaded alginate beads are shown in Fig 14. In all alginate bead experiments it is observed that the swollen beads maintained their shape even after 480 minutes.

The results obtained in this study indicate that the drug release is slow when compared with the

release of drugs from compacted pellets. In the case of alginate beads the drug release period extends to more than 8 hrs. When the ceramic and the drug mixed Sodium alginate is extruded into a solution of calcium chloride, the soluble alginate is cross-linked with calcium chloride. As a result the drug and the ceramic embedded in insoluble calcium alginate gel forms. The formation of calcium alginate reduced the permeability of the drug particles and thus delays the release of the embodied drug. It is observed that the percentage of drug release from alginate beads encapsulating the ceramic and the drug is not significantly different from the beads containing the drug only. Similar observation was encountered by Ribeiro et al (9), when they studied calcium phosphate - alginate microspheres as enzyme delivery matrices. This could be due to the fact that the drug does neither make physical nor chemical interaction with the embodied ceramic particles (Figs 5-8). The weak binding between the drug and ceramic is illustrated by the experiment carried out using compacted pellets of the drug and the carrier mixture. The Infrared spectral studies on the drug loaded ceramic containing alginate beads also indicate that there are no chemical interactions between the drug, alpha alumina ceramics and the alginate frame work.

#### **Conclusions**

The present work investigates the invitro drug release using zirconia and 4 mol% yttria stabilized zirconia drug carriers. The percentage drug release extends for 5 hrs in the case of both  $ZrO_2$  and  $YZrO_2$  pellets. The drug release profiles indicate that the mechanism of drug release may be the same except for DFH mixed  $YZrO_2$  pellet. On the other hand, the percentage drug release extends for more than 8 hrs in the case of alginate beads and the mechanism of drug release may be different with respect to the oxides as well as the drugs.

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