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New prototype assembly methods for biosensor integrated circuits

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ABSTRACT

Two new prototype assembly methods have been evaluated for biosensors that combine an integrated circuit (IC) sensor with a culture chamber. The first method uses a poly-ethylene glycol (PEG) mould to mask the IC sensor during application of a room temperature vulcanising (RTV) silicone elastomer used to insulate the bondpads and bondwires. The second method utilises the 'partial encapsulation' service offered by Quik-Pak, USA. Both methods were shown to provide good electrical insulation and demonstrated biocompatibility with the NG108-15 cell line. These methods are particularly useful for the assembly of low-cost ICs with a small (<4 mm^2) sensor area.

1. Introduction

Biosensor integrated circuits (ICs) often require demanding packaging solutions that are not readily available through the semiconductor industry. Whilst micro-electro mechanical systems (MEMS) have driven the need for new forms of packaging [1,2], there are still many applications where suitable solutions are sparse. This is discussed in [3] where it is stated, 'new or alternative packaging and assembly methods and materials are necessary for biosensors and bio-MEMES applications'. An example is cell-based biosensors based on integrated circuit technology. The unique difficulties arise from the need to enable cell culture media and buffers to contact the electrode (sensor) areas of the semiconductor die whilst simultaneously providing biocompatible electrical and chemical isolation from the bondpads and bondwires at the edge of the die. With the industry in its infancy, several prototyping solutions have been developed by researchers to meet their specific needs. Of particular merit is the method optimised by Offenhäusser et al. [4] where a customised epoxy ring is adhered between the sensor and bondpads before a potting resin or room temperature vulcanising (RTV) silicone elastomer is used to cover the bondwires. This popular approach has been further developed by Heer et al. [5] to extend lifetime up to at least three months by using EPO-TEK 302-3M (Epoxy Technology Inc., USA). These solutions appear to be well suited to ICs that have a fairly large die area compared to the sensor area. This allows for a large distance, e.g. greater than 2 mm, between the central sensor area, such as an array of micro-electrodes, and the bondpads. For example, Frey et al. [6] had a die of 48 mm^2 with sensor area of 6.4 mm^2. This allows for relatively easy/ low-tolerance placement of the epoxy ring. ICs with such geometries typically have amplifier and logic circuits in the area between central sensor and the bondpads at the IC periphery. Alternatively, Hammond and Cumming [7] and Delille et al. [8] have developed packaging solutions based on SU-8 and Loctite photo-patternable adhesives where a thick coating (~1.5 mm) exposes the sensor area whilst leaving the bondpads and bondwires coated. These photo-patternable methods are also attractive due to their simplicity and have reported to be a repeatable assembly process for cell-based sensors with a short lifetime of up to 7 days. Beyond this timescale it is reported in [7] that the SU-8 suffers excessive electrical leakage. Similarly, in [8] they found that the useful lifetime of the Loctite 3340 adhesive was one week and was incompatible with ethanol sterilisation.

This paper reports new techniques for prototype assembly in application areas that require small die sizes (e.g. <20 mm^2) and the distance between the edge of the exposed sensor and the bondpads is also small (i.e. <2 mm). With these geometries it becomes increasingly difficult to fabricate and place a thin epoxy wall between the sensor and the bondpads. In addition, the assembly method must be suitable for devices with a lifetime longer than one week. For example, our CMOS IC biosensor, featuring a reusable multiple electrode array (MEA), has a square array of 48 electrodes of 30 μm diameter with just 700 μm between the edge of the

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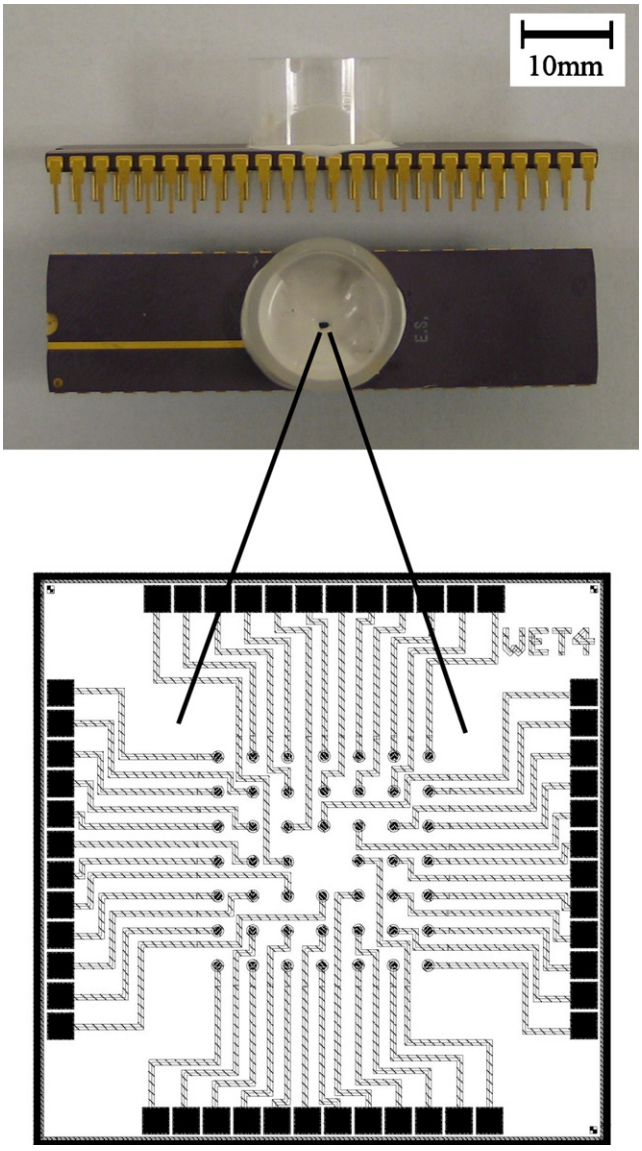

Fig. 1. Biosensor and die schematic. The photograph shows our established assembly method by manual application of Silastic 9161 elastomer. The central void in the elastomer contains the sensor shown in the IC schematic. The side dimension of this square IC is 3.16 mm. The central area of the IC is an array of 48 circular electrodes of 30 μm diameter. The square bondpads are at the periphery of the IC. The width of the electrode array is 1.2 mm with only 0.7 mm between array and bondpads.

sensor area and the bondpads. The device (Fig. 1) is being used for neuronal recordings and as an electric cell-substrate impedance sensor (ECIS) which require a cell culture duration of up to 14 days in vitro. We have therefore developed a method that builds on our experience using the biocompatible elastomer Silastic 9161 (Dow Corning, UK) combined with a simple mould to protect the sensor array. We have also evaluated a packaging solution based on the commercial 'partial encapsulation' process provided by Quik-Pak (San Diego, USA). The potential of the Quik-Pak method for biosensor applications was illustrated in [9] where an 8 pin dual-in-line (DIL) package was demonstrated to be stable for the two hours required to measure oxygen and nitric oxide release from fibroblast cells. We have extended this work by evaluating the biocompatibility of this packaging method and performing these tests at 14 days in vitro.

2. Materials and methods

Two processes were evaluated: 'mould-based assembly' and 'partial encapsulation'. The principle of the mould-based process developed in this work is to initially shield the sensor array with a water-soluble mould. An RTV elastomer is then applied over the whole chip so that it fills the cavity, covering bondwires and bondpads. The water-soluble mould is then dissolved to leave the exposed sensor electrodes. The principle of the partial encapsulation method is to adhere a frame to the IC surface that defines the sensor window, then back-filling the void behind the frame with mould compound to cover the bondwires. The following sections describe the mould-based assembly materials, the mould-based assembly process and the partial encapsulation assembly process. The electrode post-possessing and cell culture methods common to both assembly processes are outlined.

2.1. Materials for mould-based assembly

MEA ICs were fabricated by austriamicrosystems AG, Germany. Thirty devices were supplied in 48-lead ceramic DIL packages with removable die-cavity lids. For our work, a 10 mm tall glass cylinder culture chamber (QB Glass, UK) is adhered to the top of the ceramic package so that it encircles the open die cavity. A cyanoacrylate adhesive can be used for a permanent bond, or the glass adhered using Silastic 9161 (Dow Corning, UK) so that the packages can be more easily disassembled, e.g. for scanning electron microscopy (SEM) analysis.

To form the water-soluble mould, a reusable aluminium mould template was prepared using basic machine-shop tools (Fig. 2). The critical dimension is the size of the aperture at the base of the mould. Above the aperture, a conical taper was formed using a 45° countersink bit – the resulting open well shape is preferred for good cell plating, ease of microscopy and possibly better diffusion of media into and out of the well. The angle must be sufficient to ensure that the well sides cover the knee of the bondwires where they rise away from the bondpads. The mould itself was formed of polyethylene glycol (PEG) with average molar mass of 35,000 g mol^{-1} (Sigma Aldrich, UK), supplied as flakes a few millimetres in length. The mould was formed by placing the aluminium template on a glass microscope slide, heated on a hotplate to approx 100 °C and then flakes of PEG were melted into the mould. A solid core wire 'handle' was then inserted into the mould and held in position with cross-grip tweezers whilst the PEG was allowed to cool. By using a template of two halves, the mould (Fig. 3a) can more easily be released. Fillets of excess PEG, resulting from the template joint, were removed with a modelling knife.

Preliminary experiments found that the solid PEG-35,000 does not form a seal with the sensor surface which is sufficient to keep out the fluid elastomer. This was resolved by applying a thin layer of waxy PEG to the centre of the mould base (Fig. 3b). As the mould is lowered onto the IC surface the waxy PEG is squeezed and forms a tight interface. By assessing a range of compositions, a 1:1 weight ratio of PEG-1000 and PEG-1450 (Sigma Aldrich, UK) was found to be a suitable formulation, where 1000 and 1450 are the respective average molar masses (g mol^{-1}). PEG was chosen due to its good biocompatibility [10] and its low melting temperature (~64 °C for the Sigma Aldrich PEG-35,000). This enabled easy removal of the mould by melting at a temperature that is also compatible with the cured elastomer.

2.2. Mould-based assembly process

No specific equipment is necessary for the PEG process, but the mould must be positioned accurately over the sensor array during the application and curing of the elastomer. This requires some