JCTEI
JOURNAL OF CLINICAL TRIALS AND EXPERIMENTAL INVESTIGATIONS
Year: 2023 Volume: 2 Issue: 3

ORIGINAL ARTICLE

10.5281/zenodo.8236294

# A comparative cytotoxic evaluation of the bulk-fill composite resins cured with new-generation led unit at different thicknesses

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**Received:** 03 July 2023
**Revised:** 19 July 2023
**Accepted:** 24 July 2023
**Published:** 10 August 2023

**Keywords**
- Bulk-fill composite
- Cell viability
- MTT
- VALO

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## Abstract

**Objective:** Nowadays, bulk-fill composites are frequently used to restore posterior teeth. Herein, we aimed to asses the cytotoxicity of two bulk-fill composites (SDR Plus and ACTIVA BioActive-Restorative) in terms of thickness and curing device by comparing them with conventional composite (G-aenial Posterior).

**Materials and methods:** Bulk-fill composites were prepared as 4 mm layers and cured by different generation curing units; Elipar FreeLight 2 and VALO. After polymerization, 4 mm composites were divided into two by transparent strips between the layers. Each group contained six samples as total 30 samples. The samples were incubated with the cell culture medium to obtain eluates for 1, 3, and 7 days. After incubation times, eluates were added to human healthy fibroblast cells (CCD-1079Sk) for 24 and 48 hours, and cellular viability was measured through MTT method.

**Results:** In all conditions, SDR has shown the least cytotoxicity, followed by GC and ACT, respectively (cell viability; SDR>GC>ACT). Additionally, cell viability was increased over time (as 1, 3, and 7 days), and was decreased as the thickness increased. While bulk-fill resins were not affected by curing device, 3rd generation LED was better for GC.

**Conclusions:** Cytotoxicity of bulk-fill composites could alter by preparation methods. This study shows that thickness may be increased cytotoxicity for all resins, while the light source is not very effective.

**Cite as:** Susgun Yıldırım Z, Susgun S, Atasoy S. A comparative cytotoxic evaluation of the bulk-fill composite resins cured with new-generation led unit at different thicknesses. J Clin Trials Exp Investig. 2023;2(3): 144-152.

## Introduction

When developing restorative materials to be used in dentistry, in addition to properties such as resistance, aesthetics, and ease-of-use, biocompatibility must also be taken into consideration. The depth of polymerisation of composite resins is very important in biocompatibility just as in the physical properties of the material. The degree of hardening of composite resins with polymerisation with a light curing unit depends on the chemical structure of the material, the ratio of filler and the light source used (1). Irrrespective of the technique used, with developed formulas bulk-fill composites can be placed as a mass up to 4-5mm in thickness, and consequently display an acceptable degree of polymerisation transformation and controlled polymerisation shrinkage (2,3).

To increase the depth of polymerisation at this thickness, methods have been developed such as reducing the ratio of filler, increasing the filler particle size, increasing translucency and the use of additional photo-initiators (4). To achieve full polymerisation, it is important that in addition to composite thickness, light devices are selected which can produce light at a sufficient power and correct wavelength (5).

First and second-generation LED light devices cannot polymerise some composite resins as the wavelength range (450-490nm) is not appropriate. Therefore, 3rd and 4th-generation LED light devices have been developed which can form light in a wavelength range of 405-410nm (6). Like the 2nd-generation, these light devices have a blue diode and one or more low-power purple diodes. Thus, camphorquinone and other photo-initiators can be activated (7).

Systemic, allergic, and toxic reactions caused by dental restorative materials are extremely rare. However, it has been reported that allergic reactions can develop to degradation products with organic components of composite resins (8). It has been claimed that cytotoxic effects originate from residual monomers that form and can be released during or after the polymerisation of resins (9).

The aim of this study was to evaluate the cytotoxic effects of a base bulk-fill and a glass ionomer content bulk-fill composite compared with a conventional composite with the MTT method according to the different thicknesses and different generation LED curing units. The null hypothesis of the study was that the layer thickness and curing unit would have no effect on the cytotoxicity of the composites.

## Materials and methods

### Sample preparation

The properties of the composite resins are shown in **Table 1**. Titanium molds and transparent polyester strips were used for sample preparation. The mold used in the preparation of the samples is 4mm high by combining two 2mm metals with a key-lock system. These samples were divided into two by placing a transparent strip between these molds. Test samples were prepared as described below.

1) Disc I (6mm Ø x 2mm) top surface cured directly (Disc I: 0mm – 2mm)

2) Disc II (6mm Ø x 2mm) has a bottom surface, cured by LED from the top surface of disk I and the distance traveled by the light reaching the bottom surface is 4 mm in total (Disc II: 2mm – 4mm).

Two different LED curing units, 2nd and 3rd generation, were used for the polymerization of resins according to the instructions of the manufacturers (**Table 1**). Half of the resin samples were polymerized using the Elipar FreeLight 2 (approx. 1000 mW/cm$^2$, 3M ESPE, Seefeld, Germany) as 2nd generation. Under the standard curing mode, an output wavelength ranging 430-480 nm was applied. The other half of the resin samples were polymerized using the VALO (approx. 1000 mW/cm$^2$, Ultradent Products Inc, USA) as 3rd generation. Under the standard curing mode, an output wavelength ranging 385–515nm was applied. After polymerization, all samples were taken from the molds, and it was stored dry in the dark for 24 hours before analysis.

Six samples were prepared for each composite resin group (n=6). Since the bulk-fill composite samples were divided into two, a total of 30 samples were studied. The resins were cured with 2 different LED curing unit (n=3). Thus, a total of 10 experimental groups were formed as described in **Table 2**.

### Cell Culture

CCD-1079Sk cell line (human normal skin fibroblast cells, CRL-2097, ATCC, USA) was cultured in Dulbecco's Modified Eagle Medium (DMEM) (PAN-Biotech GmbH, Aidenbach, Bavaria, Germany) with 10% FBS (PAN-Biotech) and 0.2% Primocin (Invivogen, San Diego, California, USA) at 37°C in 5% $CO^2$ atmosphere with 95% relative humidity. When the cells were reached 80% confluency, they were trypsinized and counted for cell viability assay.

**Table 1.** Properties of test materials.

| | Type | Cure-time Shade | Photo-initiator | Composition of materials based on manufacturer's data | Manufacturer |
|---|---|---|---|---|---|
| **G-aenial Posterior** | Micro-hybrid | 2mm for 20s, A2 | CQ | UDMA, DMA co-monomer, (Bis-GMA free), Inorganic filler> 100 nm, Fluoroaluminosilicate, inorganic filler <100 nm, Fumed silica, Prepolymerized fillers (16-17 µm), Silica, Strontium and latanoid fluoride. | GC, Japan. |
| **SDR Plus** | Flowable bulk-fill base | 4mm for 40s, A2 | CQ | SDR ™ patented urethane di-methacrylate, di-methacrylate resin, di-functional diluents, barium and strontium alumino-fluoro-silicate glasses (68% by weight, 45% by volume), photoinitiators, colorants. | Dentsply Sirona, USA. |
| **ACTIVA BioActive-Restorative** | Flowable bulk-fill | 4mm for 20s, A2 | CQ | Mix of diurethane and methacrylates (without Bis-GMA), modified with polyacrylic acid (44.6%); reactive glass filler (21.8% by weight); inorganic filler (56% weight), patented rubber resin (Embrace), silica (~ 3.0%), sodium fluoride (0.9%), water. | Pulpdent, USA. |

*CQ= Camphorquinone, Bis-GMA= Bisphenol A-glycidyl methacrylate, DMA= Dimethylacetamide, UDMA= Urethane dimethacrylate.*

**Table 2.** Design of experimental groups.

| *Sample* | *Thickness* | *Curing Unit* | *n* | *Abbreviation* |
|---|---|---|---|---|
| G-aenial Posterior | 0-2 mm | 2nd Generation | 3 | GC2-2 |
| G-aenial Posterior | 0-2 mm | 3rd Generation | 3 | GC2-3 |
| SDR Plus | 0-2 mm | 2nd Generation | 3 | SDR2-2 |
| SDR Plus | 0-2 mm | 3rd Generation | 3 | SDR2-3 |
| SDR Plus | 2-4 mm | 2nd Generation | 3 | SDR4-2 |
| SDR Plus | 2-4 mm | 3rd Generation | 3 | SDR4-3 |
| ACTIVA | 0-2 mm | 2nd Generation | 3 | ACT2-2 |
| ACTIVA | 0-2 mm | 3rd Generation | 3 | ACT2-3 |
| ACTIVA | 2-4 mm | 2nd Generation | 3 | ACT4-2 |
| ACTIVA | 2-4 mm | 3rd Generation | 3 | ACT4-3 |

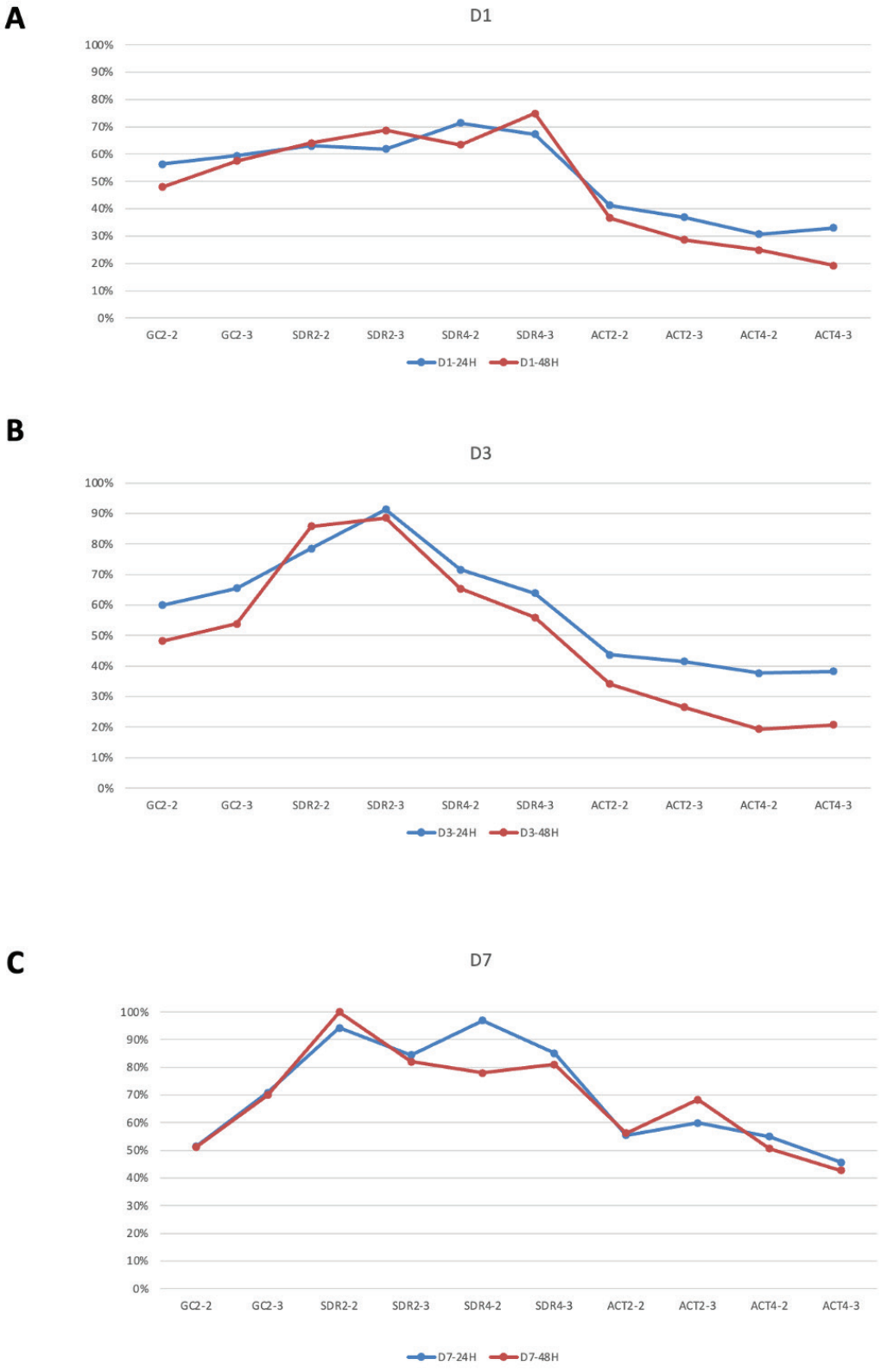


**Figure 1.** Cell viability results in CCD-1079Sk cells after exposure to different composite eluates via MTT assay for three-time points (A. Day 1 B. Day 3, C. Day 7) across two incubation times (24h, and 48h) are shown.

### Composite extracts

Before using both surfaces of composite discs were sterilized under UV light in sterile conditions at a laminar flow cabinet for 15 min and composite discs were placed in 24-well plates. According to International Standards Organization 10993 (ISO 10993-12:2012) recommendations, composite discs were incubated in culture media with an extraction ratio of 3cm2/ml for 1 day, 3 days, and 7 days. Each well containing two composite discs with the culture media was placed in the 37°C incubator for 1 day, 3 days, and 7 days. Additionally as a control group, each plate had culture media without discs as an untreated media. At the end of the each incubation period, eluates were collected from wells and used for cell viability assays.

### MTT assay

Thiazolyl Blue Tetrazolium Bromide (MTT) (Gold Biotechnology Inc., St. Louis, MO, USA) dye was prepared by dissolving in 1X PBS at the final concentration of 5 mg/ml. MTT working solution was filtered using 0.22 um syringe filter at a sterile laminar flow cabinet.

To investigate cell viability with MTT assay, the CCD-1079Sk cells were seeded into 96 well plates and incubated overnight. After incubation, culture media was aspired from wells, washed with 1XPBS and 200 ul of the composite eluates (1 day, 3 days and 7 days) were added into the wells. The control group was included containing only cells and growth media without addition of eluates. The plates were incubated for 24 hours and 48 hours. Then, MTT solution (0.5mg/mL per well) was added to the each well and additionally incubated for 3 hours. After the MTT incubation, DMSO was added into the wells and waited at 37°C for 15 minutes for solubilizing of the formazan crystals produced from cells. The absorbance of each well was immediately measured using BioTek Synergy H1 Hybrid plate reader (BioTek, Winooski, VT, USA) with a 570 nm wavelength filter. The obtained absorbance data were used to calculate % cell viability by "(absorbance value of treated cells x 100) / absorbance value of untreated control cells" formula. The assay was performed in biological triplicates.

### Statistical analysis

In the present study, whether the data were distributed normally was tested with Shapiro-Wilk test. In comparing the data with normal distribution between groups, two-way ANOVA and Tukey's multiple comparisons test was used. All statistical analyses were performed at GraphPad Prism 8.0 program (GraphPad Software, Inc., CA, USA) with a significance level of 0.05 and 95% confidence level.

### Results

In the present study, cytotoxicity of two different bulk-fill composite groups (SDRs and ACTs) were compared to conventional composite (GCs) through MTT assay at three-time points across two incubation times, the findings are shown in Figure 1. All results according to different parameters are presented in the following sections.

### Material

When the cytotoxicity of the composites of the same thickness, polymerised with the same curing unit was evaluated, SDR showed the highest cell viability at all the time points (cell viability: SDR>GC>ACT). The difference between SDR and ACT in respect of cell viability was determined to be statistically significant ($p<0.0001$).

### LED curing unit

When the effect of the curing unit on the cytotoxicity of the composite resins of the same thickness was evaluated, while no statistical significance was determined, at the D7-48h timepoint, the polymerisation of GC with 3rd-generation LED was found to be more biocompatible ($p<0.0001$).

### Thickness

When the cytotoxicity was evaluated of different thicknesses of composites as a result of polymerisation with the same curing unit, it was determined that as the thickness increased in the bulk-fill group, the cytotoxicity increased at some time points. The cell viability of SDR2-3 at the D3-24h and D3-48h time points was higher than that of SDR4-3 ($p=0.003$, $p<0.0001$, respectively). At the D7-48h time point, cell viability was higher in SDR2-2 than in SDR4-2, and in ACT2-3 than in ACT4-3 ($p<0.0001$, $p=0.0096$, respectively).

### Time

The cytotoxic effect was seen to decrease over time in all the groups, independently of thickness and curing unit. Cell viability was determined to be statistically significantly higher at the D7-48h time point ($p<0.0001$).

## Discussion

In the present study, we evaluated cytotoxicity of dental composites in terms of thickness and polymerisation devices with curing 2nd and 3rd generation light source. According to our results, tickness and LED unit can effect cytotoxicity of composites, consequently aforementioned null hypothesis of this study was rejected.

Previous studies indicated that cytotoxicity may alter by many factors such as the chemical components of bulk-fill composites, layer thickness, test concentrations, duration of polymerisation, light source wavelength and intensity of light, storage conditions after polymerisation, and the duration of exposure to the cell (10,11). Thus, we considered all these parameters when designing our study.

The ISO 10993 standard provides comprehensive guideline to select test method for evaluation biological response of dental/medical materials (12). Biocompatibility is a dynamic process that can vary depending on the time and conditions (13). In composite resins, full polymerisation does not occur in surfaces in contact with the air (the oxygen inhibition layer). Therefore, residual monomers, filler particles, and other components can be released into the oral environment with the effect of oral fluids, and cytotoxic effects can occur (14).

A few previous studies has been determined that Bis-GMA, UDMA, TEGDMA, HEMA, and MMA are expressed from the matrix structure as a result of insufficient polymerisation of composite resins (15). To increase the polymerisation depth of bulk-fill composites, the ratio of filler is reduced and the particle size is increased (>20µm) and thus the filler particle-resin matrix interface is reduced. In addition, less dispersion of the light and deeper penetration is obtained by increasing the translucency (16).

Polymerisation starts when the light source activetes the starter molecules in the content of the composite resin and free radicals form. For sufficient resin polymerisation, the light and the molecules must be at appropriate wavelengths and there must be transmission of sufficient total energy (joule/centimetre squared, J/cm$^2$) (17). First generation LED with more than one low-power LED are insufficient for polymerisation (18). Although second-generation LEDs contain one high-power LED providing higher light output, the spectral bandwidth is extremely narrow (19). Third-generation LED light devices, producing light at 385-515nm wavelength, 1000mW/cm$^2$ energy intensity, and >8W power output, are named polywave or multipeak. Therefore, it has been reported that they provide the best level of polymerisation and photoactivation of resin-based materials containing alternative starters (20). For cytocompatibility of composite resins full polymerisation must be provided, and this will be possible with the selection of an appropriate light device appropriate to the resin thickness.

In a study which investigated the effects on expressed residual monomers of different modes of 3rd-generation LED and the layer thickness of bulk-fill composite resins, it was found that standard mode produced TEGDMA, Bis-GMA, and UDMA at lower amounts in composite materials but as layer thickness increased, so the expressions increased. Therefore, layer thickness and duration of polymerisation were of critical importance for bulk-fill composites and care must be taken to follow the manufacturer's instructions (21).

On the other hand, Marigo et al. (22) reported that bulk-fill composites showed a mild cytotoxic effect despite differences in the degree of hardness and transformation, that the amount of monomers expressed was affected by thickness in each sample but was always very low, and there was no cytotoxic effect of this. Several studies have been conducted comparing the cytotoxicity of conventional composite and bulk-fill composites and cell viability of >70% has been classified as non-toxic (23,24). In a study which evaluated the physical and biological effects of various monomers in dental composites (polypropylene glycol dimethacrylate [PPGDMA], triethylene glycol dimethacrylate [TEGDMA],urethane dimethacrylate [UDMA], bisphenol A glycidil methacrylate [Bis-GMA]), it was shown that the use of UDMA and PPGDMA formed composites with excellent transformation without increasing shrinkage, cure depth and mechanical properties, and composites containing UDMA showed a little more cytocompatibility than those containing Bis-GMA (25).

Considering that Bis-GMA is more toxic, composites with content weighted towards UDMA were selected in this study to reduce the effect of chemical content on cytotoxicity. The study results showed that the cytotoxic effects of SDR were the lowest independently of layer thickness. In another study, the degree of transformation and cure depth of SDR were found to be high and there was no cytotoxicity within 24 hours (26). In addition, the effect of SDR on dental stem cells viability, cell damage or apoptosis, and mesenchymal markers expression was investigated and no significant effect was found (27). According to

the manufacturer's information, filler size is increased in SDR, and thus the filler and organic matrix interface is reduced, light dispersion is reduced, and absorption is increased. These conditions may provide sufficient polymerisation in all the layers of SDR.

The glass ionomer content, which has previously entered into reaction, found in some bulk-fill composites has been seen to result in the lowest cell viability in cytotoxicity studies (28,29). The mild cytotoxicity of the ACT group may be due to polyacrylic acid in the content.

Taken together, we investigated whether different generation curing units or thickness may effect on cytotoxicity of samples which prepared according to recommendation of manufacturer's. As a result, bulk-fill composites were not affected by the curing unit, whereas 3rd-generation LED showed a positive effect on conventional composite. Thickness constituted a more important parameter in bulk-fill composites.

In the years when LED light devices were first launched on the market, comparative studies were conducted with quartz tungsten halogen (QTH). It was reported that samples cured with QTH were less cytotoxic than those polymerised with 1st-generation LED, and the polymerisation was not sufficient (30,31). Studies in later years comparing QTH with 2nd-generation LED light devices showed that polymerisation was improved with the correct dental composite combination, and cell viability was positively affected (32-34). When the results of these studies are taken into consideration, it can be said that the light power developed over time is positively reflected in polymerisation and therefore, cytotoxicity. The heat formed with increased light power can have a negative effect on living cells, but Uhl et al. (35) reported that heat alone was not effective on cytotoxicity, and incomplete polymerisation of the composite could be more effective.

In studies researching the cytotoxicity of composites following polymerisation with 2nd-generation and 3rd-generation LED devices, Çörekçi et al. (36) reported that high-intensity plasma-like LED affected polymerisation more productively than traditional LED, and therefore higher DC rates and associated cell viability rates were seen. Photo-initiators are an important factor for photo-polymerisation. While 2nd-generation LEDs only activate camphorquinone, 3rd-generation LEDs show variability on this subject. Therefore, the composites selected in this study were appropriate to the common initiator system for 2nd and 3rd-generation devices.

## Conclusions

Despite the limitation of this study, our result supports that the curing unit may affect the cytotoxicity of conventional composite, whereas thickness may alter the cytotoxicity of bulk-fill composites. These results should be reinforced with further research and different composite samples.

## Conflict of interest:

The authors declare there are no possible conflicts of interest.


## Funding source:

No funding was required.


## Ethical approval:

Approval for the study was granted by Cukurova Unıversity Faculty of Medicine Non-Interventional Clinical Researches Institutional Ethics Committee (5 April 2019, meeting no:87, decision no:21).


## Acknowledgment:

No


## Peer-review:

Externally. Evaluated by independent reviewers working in at least two different institutions appointed by the field editor.

## Contributions

Research concept and design: **ZSY, SS**
Data analysis and interpretation: **ZSY, SS, SA**
Collection and/or assembly of data: **ZSY, SS, SA**
Writing the article: **ZSY, SS**
Critical revision of the article: **ZSY, SS, SA**
Final approval of the article: **ZSY, SS, SA**

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