REVIEW ARTICLE

CURRENT TRENDS IN DELIVERY OF AGENTS VIA DENTAL RESTORATIONS

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ABSTRACT

Agents of choice may be introduced in to the mouth via dental restorations, but this concept is only in embryonic stages and needs to be explored, modified, controlled and gauged to make it useful. This study aims at indicating the common therapeutic agents that are being delivered via dental restorations, modern restorative materials successfully delivering agents, and methods of agent incorporation; elaborating the potential for future use of such systems. Relevant publications from the last fifty years were included by searching 'dental restorations', and 'drug delivery systems' via [Mesh terminology]. Specific exclusion and inclusion criteria were set. It was found that the arena of drug delivery via dental restorations seems to be restricted to fluoride, the most commonly delivered agent via restorations. Glass ionomer cements including resin modified GICs; composites including compomers, and nanocomposites; and to some extent amalgam are the materials being researched upon. Although most research surrounds systems that rely upon recharge, modern microcapsules have been designed that can be used to incorporate the agent into the restoration. There is a dearth of work been done on the factors affecting the delivery of agents. So far, the dicalcium phosphate anhydrous (DCPA) incorporated nanocomposite is the most promising fluoride-delivering restorative material with a competent blend of fluoride releasing and mechanical properties.

DCPA-incorporated nanocomposite and ion impregnable microcapsules are new horizons for drug delivery using dental restorations.

Key Words: *Dental Restorations, Drug Delivery Systems, Fluoride release, Ion impregnable microcapsules, Dicalcium phosphate anhydrous incorporated nanocomposite.*

INTRODUCTION

Dental restorations, apart from providing treatment to oral carious lesions, have also introduced a method to import foreign materials in to the oral cavity. Whereas criticism is rampant as far as introduction of toxic substances via dental restoration is concerned, their usefulness as a vehicle to transfer beneficial and therapeutic substances in to the oral environment is comparatively somewhat unexplored.

Treatment of an oral carious lesion often precedes problems such as secondary caries. Despite numerous preventive strategies, the recurrence of caries on an already restored tooth is an episode observed frequently. Especially along the most in-demand tooth-coloured dental composite restorations, the occurrence of secondary caries is most probable, if not unavoidable. This renders dental restorative treatment only a temporary solution to the problem. Since decades, these materials have been under research for alterations that will prevent such sequalae. Most of the focus has been on the release of anticariogenic and remineralization agents from these restorations.

The challenge remains to create flexible technology that will allow controlled and long-lasting release of desirable agents from dental restorations in to the adjacent environment. This systematic review attempts to gauge the research that has been done in this area in terms of quantity and quality and to assess whether this research has been used or is expected to be used adequately.

The objectives of this analysis is to outline the major portion of research done on delivery of agents via dental restorations and to find out which therapeutic agents have been researched upon mostly so far; which modern restorative materials have successfully achieved

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this goal; what methods are being used to incorporate the agents in to the restorative material; to assess the success of any specific technologies.

METHODOLOGY

A comprehensive electronic search was conducted via PubMed. All literature published in the last fifty years i.e. from 1966 to 2015 on drug delivery systems was retrieved; there were 116744 publications. Then, publications on 'dental restorations, permanent' from the last fifty years were retrieved. There were 35352 publications. Using Mesh terminology 31 articles were found available which were specifically on dental restorations being used as drug delivery systems and they were thoroughly read through. They were further scrutinized for relevance using specific exclusion and inclusion criteria which was set as given in the Table 1.

Finally, 19 studies were included in the final analysis. Fig. 1 illustrates this process. To analyze the trend of research done on drug delivery systems over the years, a graph (Fig 2) was plotted which shows the number of papers published on the topic year-wise during the last fifty years, i.e 1965 to 2015. The findings from all of the included articles were organized in the form of a table (Table 2) given below. The results derived from this process have been discussed thereafter.

RESULTS

The amount of work being done in the area of drug delivery systems is enormous, but as dental restorations were focused, a limited amount of literature was yielded. This is elucidated by Fig 2. Restorative materials are shown to bear the potential of holding and delivering other agents, including drugs, demonstrated by the successful treatment of gingivitis with corticosteroids released by labial veneers. However research in this area is scant. Fluoride, due to its anticariogenic and remineralization capabilities, is found to be the most researched therapeutic agent that can be delivered via a restoration.

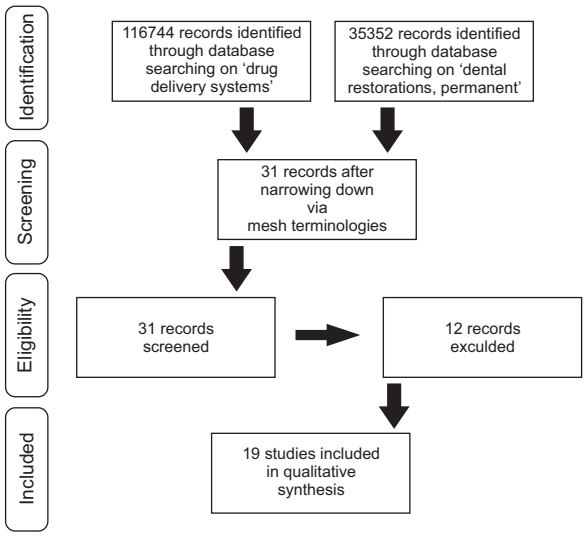

Fig 1: Flow diagram showing the methodology of selection

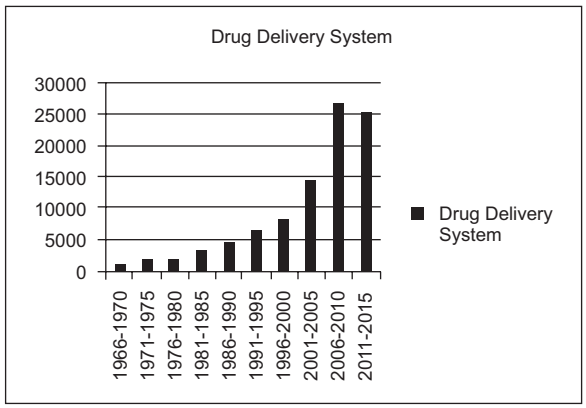

Fig 2: Trends on Research on Drug Delivery Systems

The most researched restorative material as far as drug delivery systems are concerned is GIC, whereas the

TABLE 1: ELIGIBILITY CRITERIA

Inclusion criteria	Exclusion criteria
• Drug or other therapeutic agent delivered via dental restoration	• Delivery of therapeutic agent not the subject of discussion
• Measurement/ evaluation/ quantification of efficacy of therapeutic agent being delivered	• Dental restoration not medium of drug delivery
• Assessment of method of incorporation of agent in to the restoration	• Means of drug delivery is any other than the dental restoration
• Publication dates from 1966-2015, i.e. last fifty years	• Drug being retained rather than delivered via restoration
• Abstracts plus full text articles	• Publications of or before 1965
• Permanent restorations	• Abstracts with insufficient information
	• Temporary restorations

TABLE 2: INCLUDED LITERATURE AND RESULTS

Study/ author/ year	Type of study	Purpose of Study	Agent delivered	Restorative material used and method of drug incorporation (if mentioned)	Relevant Findings	Conclusive remarks and recommendations for future research
[1] Chandra, Pandurang et al. 2004	Case report study	To test drug delivery via veneers	Topical corti-co-steroids	Acrylic	Evidence for potential of labial veneers to deliver drug	Potential of acrylic to deliver agents to treat oral diseases should be analyzed via case control trials
[2] Davidson, 2012	Exp, in vitro	Introduces ion impregnable microcapsules	K2H-PO4, Ca(-NO3)2 or NaF	Non-specific Ion permeable microcapsules	Release rates increased with the initial concentration of salt solution; fastest: NaF, slowest: K2H-PO4; monomer of capsule affected ion release at 3.0 M.	Effects of temperature, membrane thickness, hydrocarbon length, choice of counter ion, and other factors affecting efficacy should be investigated
[3] Xu, 2010	Review	Reviews nano-composites with CaPO4 and F fillers	CaF2 to release F ions	Nanocomposite containing nanoparticles prepared by spray-drying; nanoparticles fused onto ceramic whiskers	High surface areas of the nanoparticles enables increased amount of ion release at low filler levels	Lower filler content may affect strength bearing properties. If strength properties match requirements, may be considered for trials
[4] Shashibhushan, 2008	Exp, in vitro	Compares anti-bacterial properties of F and Zn releasing GICs	F	Glass ionomer cements	F releasing GICs have anti-microbial properties; Fuji II Light Cure has highest degree.	Antibacterial activity related to F release but not Zn release
[5] Al-Naimi, 2008	Exp, in vitro	Studies effect of F release on saliva and biofilm	F	Glass ionomer cement (GIC), resin modified glass ionomer cement (RMGIC), compomer, giomer and composite	GIC released more F than the Composite, Giomer and Compomer but for short time; did not affect bacteria and biofilm; high releasing GIC have the lowest resistance to bacterial proliferation in neutral saliva	Suggests that either fluoride is not a dominant factor in controlling biofilm formation or its concentration is too low to be effective
[6] Xu, 2007	Exp, in vitro	Develops strong composite with Ca, PO4 ion release	Ca and PO4	Nanocomposite. DCPA nano-particles (spray-drying technique in laboratory) with nano-silica-fused whiskers as fillers in resin matrix	Ion discharge increased with decrease in DCPA particle size; whisker reinforcement increased the composite strength	Nano DCPA-whisker may promise the combination bearing stress-bearing and caries-inhibiting capacities

[7] Ozdemir-Ozenen, 2013	Exp, in vitro	Studies effect of single fluoride gel application on surface properties	F	GIC restorative material, nanoionomer/ resin modifies glass ionomer, GIC core build up material, compomer	1.23% APF gel significantly increased the surface roughness of GIC based materials	Recharge using F gel may be detrimental to surface properties. Other methods of F uptake should be developed
[8] Xu, 2003	Exp, in vitro	Studies compressive strength, F discharge, recharge of15 commercial materials	F	Glass ionomers, resin-modified glass ionomers, compomers and composite resins	Recharge/release decreases compressive strength and other mechanical properties	F exchange instead of fluoride release should be developed
[9] Preston, 2003	Exp, in vitro	Studies recharge of esthetic materials over two years	F	Glass ionomers , resin-modified glass ionomers, compomers, composites	Recharge potential of GICs is the highest and that of composites is almost negligible	Author suggests use of GIC materials in patients with high caries rate
[10] Guida, 2002	Review	Reviews F releasing properties of GPACs	F	GPACs: particle reinforced polymeric composites	Commercial products studied which have varying composition	Further research warranted
[11] Forss, 1995	Exp, in vivo	Studies effects of old GIC fillings on plaque	F	GIC	F concentrations in plaque of old GIC fillings slightly increased; no effects on cariogenic organisms.	Aged GIC restoration do release beneficial amounts of F
[12] Dijkman, 1993 #28	Exp, in vitro	Studies F release and demineralization statistics correlation	F	Fluoridated composites	Data predicts F release of about 200-300 µg/cm2 over 1 month would inhibit secondary caries	Development of controlled release of F from these composites to prevent secondary caries
[13] Dijkman, 1992	Exp, in situ model	Studies recurrent caries with F releasing composites	F	Fluoridated composites	Enamel demineralization reduced after 1 month in artificial gap; beneficial effect larger in the gap	Prevention of demineralization in gap due to contraction gap may prevent secondary caries; trials must be done
[14] Garcia-Godoy, 1991	Exp, in vitro	Studies F release in GIC lined amalgam restorations	F	Dispersalloy amalgam, with 1 mm of Ketac-silver on axial wall, with GC lining, with miracle mix;	Miracle Mix and GC Lining released more fluoride than Ketac-Silver lined amalgam restorations over 1 year	More F releasing base material should be encouraged
[15] Triolo, 1991	Exp, in vitro	Studies F release in core build-up materials	F	Conventional composite core build-up paste, fluoridated core build-up paste, glass cermet	Lesions were more profound for conventional composites than for the other two	F release by core build up material retard demineralization, further research warranted

[16] Hatibovic-Kofman, 1991	Exp, in vivo and in vitro	Studies F discharge in GIC	F	GICs	GIC can be recharged using F toothpaste, levels high after 1 year	Toothpaste an efficient recharge option; must be further researched
[17] Skartveit, 1986	Exp, in vivo	Clinically assesses F incorporated amalgam	F	Fluoride-containing amalgam	Slightly better margins than the conventional amalgam after 2 years	Mechanical properties must be studied before suggesting clinical use
[18] Tinanoff, 1986	Two clinical studies	Tests safety and antibacterial property of SnF2	F	SnF2-polycarboxylate cement	Salivary concentrations increased; urinary, just over normal; gingival irritation; S.mutans levels declined	Improvement warranted by including more teeth and restrict gingival contact
					Evidence for safety and efficacy of SnF2 polycarboxylate cement	
[19] Shen, 1985	Exp, in vitro	Tests delivery in gap between tooth and restoration	F	Composite	Rate and duration were independent of the type of composite	The benefit is in its ability to maintain a high concentration of F within the gap

most successful one is dental restorative composite with its recent advancements, yielding resin modified GICs, compomers, nanocomposites, and strong nanocomposites with DCPA (Dicalcium phosphate anhydrous) incorporation. Nanocomposites have been altered to qualify as successful delivery agents by adding fluoride salts as fillers. The caries inhibiting potential of these materials vs. conventional composite can confirmedly be shown by an in vivo comparison.

Most of the research does not point out a method of incorporation of therapeutic agent in to the material. GIC fluoride release is dependent upon recharge phenomenon, considerably maiming it utilizability. So far, a reasonable method of incorporation has not been established for GIC and thus, their fluoride release continues to be of menial, if not negligible, importance.

Ion-permeable microcapsules which can contain and release agents in a controlled manner, could serve as a breakthrough for the use of dental restorations for delivery of agents.

DISCUSSION

In view of the fact that drug delivery systems are so essential to healthcare profession, it is no wonder that research in this area is abundant. Fig 2 shows that during the last fifty years there is a rising trend of number of articles published on drug delivery systems. However, when the search was narrowed down and literary work on "dental restorations" and "drug delivery systems" was retrieved, only thirty one publications were found available. This mirrors the fact that research concerned with the use of dental restorations as drug delivery systems needs more attention and has a lot of room for addition and improvement.

Nevertheless, much of the work appears to be promising for future use, for example, the use of labial veneers to deliver corticosteroids[1] shows that there is immense potential for acrylic materials to hold and deliver drug, and surprisingly this area is profoundly under researched.

Fluoride

It appears from the analysis that the most tested therapeutic substance using dental restorations as delivery system is fluoride; the benefits of which are well-established in literature. Apart from the capabilities of reducing enamel demineralization adjacent to filling[3], and causing remineralization[2,3]; and possession of antibacterial properties[4,18], it also has the tendency to prevent recurrent caries.[6,12,13] Not only as restorations[12], but also as core build up components[15], and intracoronal devices using cements[18], fluoride-releasing materials have shown to be beneficial. Tin fluoride (SnF2) polycarboxylate cements causes gingival irritation along

with raised salivary fluoride content[18], implying that these materials need to be investigated as far as safety and efficacy is concerned.

The Future of GIC related Fluoride release

Although maximum studies on dental restorations as drug delivery systems were found encircling GICs and their fluoride release, this property has failed to be very exciting, as its usefulness is limited by its dependence on the recharge phenomenon: GICs require an external source of fluoride to pump the resoration with it so that it can slow-release it later. Considering GICs are found to have the highest and composites the lowest recharge potential among esthetic materials, the use of GIC materials in patients with high caries rate is suggested.[9] In any case, the beneficial effects of fluoride depend upon the recharge potential and it is more important than the release rate.[8] Although gels can be used to increase diffusion gradient of fluoride in saliva vs. restoration causing recharging of the GIC, this does not wrap up the problem as these gels also affect surface properties negatively (roughening). This establishes further problems with the GIC which overshadow its fluoride releasing benefits.[7] Another useful recharge vehicle can be fluoridated toothpaste as presented in an in vivo study, high fluoride values were demonstrated in the saliva even after one year.[16] Nonetheless, no comments have been made on the effects of this toothpaste on surface properties and this needs to be explored.

Compressive strength decreases with the increase in the release rate of fluoride ion so a compromise is made on the strength of restoration as we move across the spectrum from low releasing materials towards high releasing materials, and from amongst them, resin modified GICs seem to be the most well-balanced in strength properties vs fluoride releasing properties.[8] Still, GICs can not match the mechanical properties of classic restorative materials i.e. amalgam and composite. Achieving the mechanical perks of amalgam restorations along with the benefits of fluoride release in one restoration could be a breakthrough in retorative dentistry. Measurable amounts of fluoride are liberated from glass ionomer lined amalgam fillings, particularly from Miracle Mix and GC lining[14] and this assembly could be a successful drug delivery system for caries prone individuals, bearing the best of both worlds.

Anticariogenic and antibacterial properties

A comparison of different products of GIC for their antibacterial properties due to zinc and fluoride release yeilds that from amongst Fuji II Conventional (type II glass ionomer), Fuji II Light Cure (type II Light Cure), and Fuji IX, Fuji II Light Cure showed the most antibacterial activity. It also shows that as fluoride release increases, so does antibacterial capabilities, however zinc release does not seem to affect antibacterial properties.[4] On the other hand, in another study, while different materials including glass ionomer cements, resin modified glass ionomer cements, compomer, giomer and composites are being compared, the material with the highest fluoride release, GIC, seems to have the lowest antibacterial potential.[5] This is an interesting controversy. In vivo experimentation on patients with three year old GIC fillings reveals that although levels of fluoride in the adjacent plaque were increased, the cariogenic microflora seemed unaffected, even after topical application of fluoride gel.[11] Conversely, fluoride releasing SnF2 polycarboxylate cement has proved to possess abilities to suppress bacterial growth.[18]

It can be deduced from these results that although fluoride itself does, atleast in the long term, fluoride releasing GICs do not have much anticariogenicity. This may be due to a lack of control on the amount and rate of fluoride release. Conclusively, GICs must further be evaluated and modified to fully utilize their fluoride releasing capacities.

Fluoridated Composites

The poor performance of fluoride as an anticariogenic agent in GICs should not affect our faith in the benefits of fluoride as numerous studies have advocated fluoride release as a favourable property.[2-4,6,12,13,18] In this regard, fluoridated composites seem to be superior, as some inhibition of caries has been documented in literature; in fact, a theoretical value of 200-300 micrograms per centimetre square from a fluoridated composite over one month has been derived which is expected to cause complete inhibition of caries.[14] This inhibition may be related to reduction in enamel demineralization that seems to be to be more profound in the gap that forms in composite fillings due to shrinkage, and it is possible for a high fluoride concentration to be maintained within the gap[19] leading to inhibition of secondary caries.[13]

Nanocomposites and Compomers

Composite itself is thoroughly being explored as a delivery system. It possesses an adequate balance of mechanical properties and release of agent as these two characteristics have been found to oppose each other; i.e as the delivery of agent is improved, a decline in mechanical properties has been observed. Novel calcium phosphate and fluoride nanoparticles have been created and incorporated as fillers within the nanocomposite structure. Recent formulations consist of nanoparticles of composite along with two types of fillers: one a calcium salt, and the other a silica-ceramic whisker configuration to enhance stress-bearing capability. It was found that the increased surface area of nanofillers allowed for

more filler to be incorporated, and fillers of both types have been used to harvest this advantage. Nanocomposites bear a lot of room for filler particles, and this has been used by various researchers, varying the filler and adjusting properties. The addition of these salts yeilded successful delivery systems. However, filling the structure with these salts will take up the space for strength-bearing filler, decreasing its overall content. Silica nanoparticles fused on ceramic whiskers have been used to balance out the void in strength-bearing properties.[3] The most appropriate balance of these two fillers in the final nanocomposite structure is the most imporatant aspect that needs to be explored.

This has been done by the same group and published[6] in which nano-particles of dicalcium phosphate anhydrous (DCPA) have been synthesized and incorporaed in to dental resin. In an attempt to find a perfect blend good mechanical properties as well as considerable caries inhibiting properties due to calcium and phosphate release, it has been concluded that decreasing DCPA size increases ion release, whereas whisker reinforcement improves strength 2-3 fold. Using these results, a fairly anticariogenic strength bearing composite may be formulated and used in clinical trials.[6] Furthermore varying the ion can also be considered.

Another promising material within the caries inhibiting composites bracket is compomer.[8] In vivo comparisons can quite elucidate the efficacy of different types of composites vs each other.

Particle reinforced polymeric composites

Particle reinforced polymeric composites, also known as GPACs, which contain degraded residual glass containing a silicious layer that reinforce the polysalt matrix for improved mechanical properties, have also been studied for fluoride releasing capabilities, but these studies have been performed on commercial products[10] only and thus there is room for studying the inherent fluoride releasing phenomenon.

Potential of Amalgam of Fluoride release

Although the issue of secondary caries is not very rampant compared to composites, amalgam has also been modified and tested. Fluoride containing amalgam restorations had slightly better margins in vivo than conventional amalgam after two years.[17]

Ion Permeable Microcapsules

The need for a reliable and controllable method to release therapeutic species in to the oral environment is compounded by the frequency of occurrence of secondary caries. Recently, microcapsules have been designed and different parameters surrounding their workability have been studied. These are ploymeric (polyurethane) in nature synthesized by a heterogenous polymerization technique, the final product being capsules of a range of 1-2 µm containing potassium, phosphate, nitrate, calcium, sodium and fluoride salt solutions. These include ions that contribute to the process of remineralization. This suggests a potent method to supply ionic species to the oral environment, simultaneously controlling parameters such as bioavailability. The authors suggest the use of these devices with tooth-coloured restorations. This is reasonable as the problem of secondary caries occurs mostly with dental composite. The authors were successful in establishing functional ion release. The effects of various variables on the release rates of calcium, fluoride and phosphate ions have been appreciated and therefore release rates of these ions can be controlled by changing the concentration and nature of salt within microcapsules and structure of membrane. Conspicuously, however, the effect of temperature changes, membrane thickness, and hydrocarbon chain length variation still need to be identified[2]; the presence of counterion and factors that affect its concentration and release rate; availability of counterion in the oral environment and control of this availability are also important unexplored areas.[2] Therefore, further investigation is warranted before use of these capsules as mineralizing agents in composite restorations can be considered as suggested in literature.

CONCLUSION AND FUTURE RECOMMENDATIONS

It can be deducd that GICs and their fluoride release are the most researched topic under this heading, nonetheless, they still need to be developed due to their dependance on recharge phenomenon and poor mechanical properties. The potential of DCPA-incorporated nanocomposites as succesful tooth-coloured restorations which considerably prevent secondary caries should be researched esp. in vivo. Also, the potential for restorative materials to deliver drugs should be fully utilized and researched upon. Ion permeable microcapsules could be an advantageous method of drug incorporation. It is recommended that factors affecting drug release be studied via in vivo experimentation concerning these technologies before they are introduced in to the clinics. Despite the work being done of fluoride, a black hole exists as far as research on other therapeutic substances is concerned; and it is recommended that this area be explored because drug delivery is a potent quality of dental restorations that could be of great clinical value.

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