Project A

TITLE:

DESIGN & FABRICATION OF 3-D PRINTED MICRONEEDLE DECORATED PATCHES

INTRODUCTION:

Most individuals naturally generate adequate amounts of vitamin D through ordinary dietary intake of vitamin D (in some foods like eggs, fish, and cheese).

Conversely, vitamin D deficiency can often occur from a combination of insufficient exposure to sunlight, improper dietary intake of vitamin D, genetic anomaly could also be a potent reason along with endogenous vitamin D receptor, or even severe liver or kidney disease. Such deficiency is known for resulting in conditions like osteomalacia and osteoporosis, low bone density and rickets as well, all of which reflect inadequate mineralization of bone, enhanced compensatory skeletal demineralization, resultant decreased calcium ion blood concentrations, and increases in the production and secretion of parathyroid hormone. Increases in parathyroid hormone stimulate the mobilization of skeletal calcium and the renal excretion of phosphorus. This enhanced movement of skeletal calcium towards depreciated bone conditions. Ordinarily, while vitamin D3 is produced naturally via photochemical processes in the skin, Alendronate sodium, sold under the brand name Fosamax among others, is a bisphosphonate medication used to treat osteoporosis and Paget's disease caused due to above or any other reasons. It is an oral dosage form. Use is often recommended together with vitamin D, calcium supplementation, and lifestyle changes.

THERAPEUTIC APPROACHES OF VITAMIN D

Vitamin D supplementation is safe and inexpensive, but vitamin D deficiency often remains undiagnosed or is undertreated. Possible explanations for this disparity include the recommended age-dependent adequate intake of vitamin D was established before publication of studies suggesting that 25(OH)D levels of greater than 30 ng/mL are needed to ensure PTH suppression into the normal range

The current AI for vitamin D can easily be met by diet and/or a daily multivitamin, but this intake level may still be inadequate to reach optimal levels in many people, especially those at risk; and physicians may be uncomfortable recommending larger doses of vitamin D.

That fear is generally unmerited given the dearth of reports of vitamin D toxicity compared with the expansive literature on vitamin D deficiency. The rarity of reports of vitamin D toxicity can be explained in part by the kidney's ability to limit production of active calcitriol.

Increased calcitriol levels inhibit PTH both directly (through the vitamin D response element on the *PTH* gene) and indirectly (by increasing intestinal calcium absorption), causing calcitriol production in the kidney to decrease. Renal 24-hydroxylase activity further limits the availability of calcitriol by creating inert metabolites of both calcitriol (1, 24, 25-trihydroxyvitamin D) and calcidiol (24, 25-dihydroxyvitamin D).

The 24-hydroxylase gene is under the transcriptional control of calcitriol, thereby providing tight negative feedback.

OBJECTIVES:

It was decided to develop a site-specific formulation of a Combination of vitamin D with efficacious anti-resorptive drug, alendronate sodium with the following **objectives:**

1. To develop a site-specific formulation of vitamin D with an antiresorptive drug Alendronate sodium
2. To optimize a formulation and process for printing micro needle-based site-specific delivery system of Vit D and Alendronate Sodium by three D printing
3. To Evaluate printed micro needle-based site-specific delivery system by in vitro methods

Help in developing a system to increase the bioavailability of vitamin D and increase its absorption by treating vitamin D deficiency

MATERIALS and METHODS:

CHEMICALS:	**SOURCE:**
Cholecalciferol	Sigma Chemicals
Alendronate sodium	IPCA Laboratories
PLC	YARROW chemicals, MUMBAI
Polyethylene glycol	YARROW chemicals, MUMBAI

HPLC grade Acetonitrile	LOBA chemicals
0.01N Hcl	LOBA Chemicals
HPLC grade Methanol	SD fine chemicals
Tween 80	SD fine chemicals

DEVELOPMENT OF FORMULATION:

Preparation of formulation: vitamin-D and alendronate sodium micro-particles were prepared in the following manner. 5mg alendronate sodium was weighed and then mixed in 5ml distilled water. The mixture was then vortexed. 5mg of Vitamin D was dissolved in 5ml of DCM and then vortexed. 1mg/ml PLGA was prepared by weighing 5mg PLGA and 5ml DCM and then kept aside.

The content of alendronate sodium was dispersed in 5ml PLGA solution and then mixed vigorously. 0.3% pva was prepared using 30mg of Poly vinyl alcohol in 10ml of distilled water. After the PVA was dispersed and solubilized uniformly the mixture of PLGA and alendronate sodium was dispersed with the help of a micropipette, by dispersing small drops until all the solution is dispersed uniformly.

The RPM was set from 800-1000 RPM. Upon full dispersion the particles were dried using a lyophilization technique and weighed. The micro-particles were then observed under a microscope to determine whether the size was in the prescribed range or not.

OPTIMIZATION OF FORMULATION:

Now the formulation that was prepared earlier, was used to characterize 13 given formulation ratios using QbD analysis and the ratio of polymer and PLGA was altered to get the best formulation.

RESULTS:

The drug vitamin-D was supplied by Roche Pharma (India) and the drug Alendronate sodium was supplied by Cipla pharma, New Delhi and excipient supplied by Birmingham polymers, India and S. D. Fine Chemical, India matches the standards prescribed in official compendia for identification and purity.

The IR spectrum shows presence of different functional group, which were identical to the spectra of reference drug given in literature. Developed analytical method was repeated via UV-spectroscopy. Calibration curves were prepared in distilled water, methanol at lambda max 264.5nm, 472nm respectively with R2 value 0.9. Partition coefficient and solubility of drug was determined.

The formulation of microparticles was based on various characterization parameters like FTIR, clarity, pH, DSC used in this formulation have attracted significant interest in recent years in preparing sustained and controlled release of drugs by using physical or chemical methods. Due to its muco-adhesive property it can interact with the opposite charge of the residue in the mucus layer, which can modify mucocliliary transport system.

The Prepared micro-particles were characterized for physicochemical characteristics using TEM, Entrapment efficiency, swelling index.

TEM images show the particle surface morphology and confirms the size of particle to be round 100 nm. The entrapment efficiency of developed formulation was 92.84 ± 2.8. In-vitro drug release was found to follow Higuchi model and maximum drug release from the particles with a span of 7 days. The in-vitro drug release studies were also performed and were giving sustained release as it was demanded from the formulation

Thus, our finding suggests that a developed formulation could be established for implant therapy. It's pre-clinical and clinical applications in the treatment process need further explanation.

The present research work attempted have shown to an extent of satisfactory result for the formulation of Vitamin-D Alendronate sodium micro-particles for dental drug delivery even with the few studies and able to provide delivery of the drug to site of action and assures the presence of dosage form at the site of absorption throughout the release which is sustained.

IMPACT OF THE RESEARCH IN THE ADVANCEMENT OF KNOWLEDGE OR BENEFIT TO MANKIND:

Most dental professionals are already using the technology of the future today. 3D printing can significantly improve the workflow in any dental practice or laboratory and can drastically reduce patient chair time. It offers flexibility in product customization and superior quality and accuracy

in 3D-printed dental models. Although it was once unimaginable, dental professionals can now print occlusal splints and other dental models in-house in only a day. This not only helps to generate profit but also facilitates dental treatment. With 3D printing, there is always a place for continued development. Every software release or update enhances the hardware and offers new and exciting features. There are constant innovations in 3D-printing materials to provide users with a growing list of indications, and 3D printing can be easily integrated into the workflow of any dental practice or laboratory.

Some of the 3D-printing technologies that are currently available and used in the dental industry include digital light processing, selective laser melting, stereolithography and fused deposition modeling. All areas of dentistry are covered by 3D printing, including printed study models, surgical guides, metal frameworks, dental prostheses, temporary crowns and bridges, permanent restorations, occlusal splints, aligners, and removable dentures.

The advantages of 3D printing over CAD/CAM technology:

3D printing, or additive manufacturing, consists of adding material. In contrast, milling is a method that involves subtracting material. Labor told DTI that additive manufacturing is more cost-effective than subtractive computer-aided manufacturing and explained that it produces less waste. Additionally, 3D printing is highly accurate, faster for many indications and offers increased production efficiency since the user can produce printable solutions in volume.

Investing in new technology is a way of reaching and establishing high standards of patient care. As Patrick Thurm, the managing director and general manager for Europe at SprintRay. noted, dentists and laboratories are currently seeking efficient solutions for their practices and their patient’s post-pandemic, and a 3D printer, such as the one from SprintRay, could be a great asset to dental practices, laboratories, and patients.

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