Heliyon 9 (2023) e16476

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Assessment framework for the selection of a potential interactive dressing material for diabetic foot ulcer

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ARTICLE INFO

Keywords:
Diabetic foot ulcer
Wound dressings
Hydrogel matrix
Graph theoretic approach
Material's assessment
Drug carriers

ABSTRACT

Diabetic foot ulcer is a chronic health issue leading to lower leg amputations in approximately 15% of patients with diabetics. There are many factors directly or indirectly involved in the physiology of wound healing but being a multisystem disorder, wound healing in diabetic patients retard or worsen with heavy exudates and severe microbial infections. Wound management is of prime importance and is an emerging area to incorporate wound regenerative materials in natural or synthetic dressing materials along with proper microbial control. The article aim to identify suitable dressing materials which exhibit inherent wound healing properties at the same time flexible to be used as drug carriers for slow, consistent and effective delivery of 'functional drugs' to the wound environment. The authors selected nine materials from the popular and well accepted dressings of patient choice, analyzed them using graph theoretic approach and ranked them on the basis of graph index values obtained. A critical review has also been done on the basis of their ranking, providing insights to the advantages, disadvantage and potential of top 5 ranked candidate materials. Alginate, Honey, Medifoam, Saline, and Hydrogel dressings were the top five candidate materials ranked respectively, even then, the authors suggests that 'modified hydrogels' can have the potential to be used as a future candidate in DFU treatment as it is the only material (among the top ranked ones) which can effectively used as regenerative drug carrier, while providing all other wound healing properties in relative proportions. The proposed framework can be modified and applied in the selection and ranking of materials for any kind of applications both in industry and medical fields by identifying factors influencing the final outcome of study and by listing the characteristics of the materials selected.

1. Introduction

Diabetes, being a multisystem disorder, the physiological changes due to diabetic conditions often retard the process of wound healing in patients. A small foot sore in a diabetic patient can lead to amputation by progressing through various stages of diabetic foot ulcer and according to a meta-analysis, it has been reported that in patients with diabetes, lower limb amputation are reported to have in 19% of the patients [41, 45]. Diabetic patients are at an increased risk for wound complications due to decreased blood flow, peripheral neuropathy and many more physiological complications leading to slow wound healing.

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https://doi.org/10.1016/j.heliyon.2023.e16476
Received 19 October 2022; Received in revised form 14 May 2023; Accepted 17 May 2023
Available online 22 May 2023

1.1. Factors contributing to the onset of chronic diabetic wound infections

Diabetic wound healing is a complex process, characterized by a chronic infection phase. There should be a synergy between biochemical mediators and inflammatory cells in DFU, stimulated by different factors. In Diabetic Foot Ulcer (DFU), the distribution of repairing macrophages (M2φ) or inflammatory macrophages (M1φ) phenotypes are altered compared to the process of normal wound repair. The conversion of Monocytes to tissue regenerating phenotype of Macrophage M2 is a critical step in the tissue regeneration and repair process. Peripheral neuropathy, microangiopathy and inadequate venous circulation in the lower extremities, and hyperglycemia worsen the diabetic foot condition. More over focal points on foot, wound infections, and excessive exudates limit the regenerative potential of the wound tissue as it increases the inflammatory phase of wound and impair the macrophage phenotypic conversion in to the regenerative macrophage type M2. Lack of factors necessary for the normal healing process, like regenerative cytokines, matrix metalloproteases (MMPs) lead to impaired collagen accumulation and downregulation of neuropeptide expression and thus, reduced proliferation and migration of fibroblasts and keratinocytes to the wound site are common in the development of DFU [46]. The decreased renal function, poor nutrition and smoking or drinking habits are some of the additional contributing factors for the development of chronic DFU [3,22].

Generally, diabetics weakens the immune system. As the natural wound defense and repair are malfunctioning, bacterial colonization may occur which is further aggravated by reactive oxygen species (ROS) produced at the wound site [30].

1.2. Current strategies of diabetic wound dressing

The widely used wound management strategy in diabetic foot ulceration is wound dressings (Fig. 1). Ideally, dressings should provide wound protection by alleviating symptoms, and promote healing. No single dressing meets all the requirements of a diabetic patient with an infected foot ulcer. Dressing's research is generally poor and ideal dressings with the mentioned properties are yet to come. However, every individual dressing has its own characteristics that aid its selection. The following authors provide critical reviews on the currently used diabetic wound dressings and their advantaes and disadvantaes [4, 27, 33, 47].

Low adherence dressings like foam dressings are simple, hypo allergic and inexpensive; but they have only minimal absorbance, so frequent dressing changes may require which are painful to the patient. Hydrocolloids and hydrogels are both good absorbing materials which aid autolysis and provide sufficient moisture to the wound so that they can be used for necrotic wounds also [15]. But they are non-microbial and due to the moisture content, they attract infectious pathogens to the wound which is damaging to the curing process.

Foam dressing can provide a thermal insulation to the wound also it is of high absorbance, but they may adhere to wound making it tough to remove the dressing material [16, 29]. Alginates are another material of high preference which are bacteriostatic, hemostatic and highly absorptive in nature; can apply contouring the wound; but may need wetting before removal [14].

In addition to the above-mentioned preparations, antiseptic preparations of iodine or silver impregnated dressings like hydrofibre-Ag (silver) dressings and beta foam dressings are of common use with high antimicrobial property, moderate absorbance capacity, but without any regenerative advantages [26,48]. Moreover, Iodine may create allergies and also cannot be applied in thyroid conditions and in pregnancy.

In addition to the traditional wound dressing materials, advanced treatments like growth factor therapy, plasma therapy etc have emerged as a boon which regenerate the wound tissues, but they all require dressings along with regeneration therapy to manage wound closure and are highly expensive.

Currently, nanomaterial-based treatments are emerging using nanoemulsions, nanoliposomes, nanofibers etc. Moreover, nanomaterial based antibacterial hyperthermia therapy and gene therapy are also under development for DFU [36,46].

To provide growth factors or regenerative drugs to DFU, along with the dressing material will be an expensive treatement. A dressing material which provides a regenerative property is still in hypothesis and such a combination if materialized will be a blessing to all those who are denying the efficient growth factor treatments only because of their high cost. The cost of treating chronic wounds

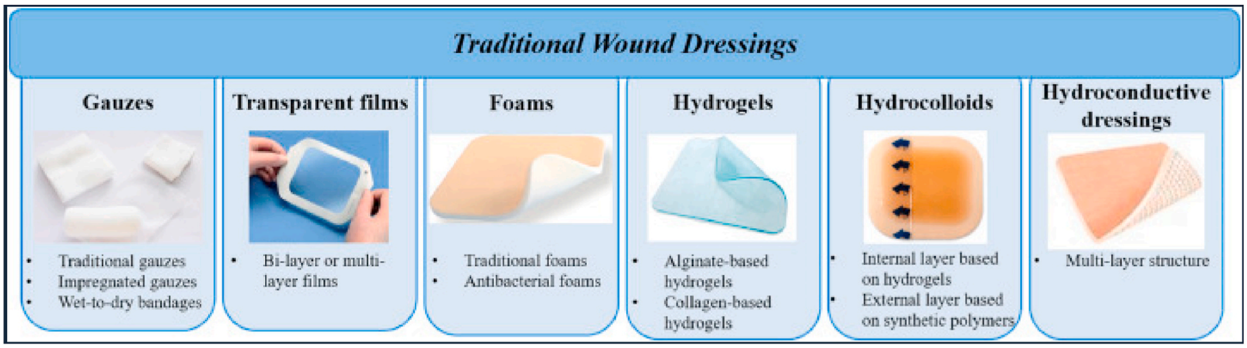

Fig. 1. Some of the commonly used traditional wound dressings for DFU (*Picture courtesy* [36].

Table-1
Identified major factors influencing DFU wound healing.

Sl.No	Factors	References
1	Wound Healing Property (F1)	[2,12,37]
2	Mechanical Protection (F2)	[12,34,37,51].
3	Cyto compatibility/toxicity to Healthy Tissues (F3)	[9,18,46]
4	Exhibits Anti-Microbial Property (F4)	[7,18,43]
5	Patient Acceptability (F5)	[11,17,40]
6	Cost – Effectiveness (F6)	[5,34,46]
7	Biocompatibility and Stability (F7)	[7,18,46]
8	Active Drug Delivery System (F8)	[11,34,37,46]
9	Anti-Inflammatory (F9)	[5,18,46]
10	Wound Regeneration Property (F10)	[2,34,46]

Secondly, widely used dressing materials of DFU were chosen for the graph theoretic analysis of its performance evaluation and ranking. Table-2 depicts the specific dressing materials for DFU dressings (Up to Grade 2 DFU).

with advanced wound care technologies keeps the general public away from such new generation therapies, so, the development of a low-cost material providing the advantages of a growth factor treatment is the need of the hour [21].

2. Methodology

Factors influencing the wound healing properties of diabetic foot ulcers have been selected, categorized and grouped in to 10 major factors and it depicts in Table 1. The commonly used and most preferred wound dressing materials have been analyzed and selected 9 materials out of it. The selections were made based on literature reviews and expert's opinion. Fig. 2 depicts the flow of selection and ranking process.

2.1. Selected factors for mathematical modelling

1. Wound healing property: The material should provide a moist environment, allowing gaseous exchange supporting cell proliferation, cellular migration, and re-epithelialization.
2. Mechanical protection: Providing physical wound protection, nonadherence to the wound, enabling the absorption of excess exudes at the same time maintaining optimal water permeability and wound protection.
3. Non-cytotoxic to healthy tissues: The material should not release toxic compounds or without generating Reactive Oxygen Species (ROS) and better to be non-Immunogenic.
4. Anti-microbial property: Diabetic foot ulcer often produce heavy exudates leading to severe microbial infections; so, the material should exhibit anti-fungal and anti-bacterial properties.
5. Patient acceptability: It is an important factor, which depend on how long the dressing material can be kept or how frequent change is needed along with ease to use and cost.
6. Cost – effectiveness: The degree of efficiency of dressing material in relation to its cost.
7. Biocompatibility and stability: The material should be stable in contact with body fluids and resistant to enzymatic degradation, also it should be biodegradable.
8. Active drug delivery system: A good quality dressing material with drug carrying capacity for targeted drug delivery and slow and consistent release of drug is an advantage to use as a drug carrying dressing material.
9. Anti-inflammatory: There should be a reduction in Cytokine release, macrophage aggregation and phenotypic conversion lowering inflammation and oedema
10. Wound regeneration property: An ideal material should stimulate angiogenesis and neuronal regeneration by inducing growth factor release from the fibroblasts and by stimulating homing of stem cells in the wound site which leads to regeneration of endothelial cells and other wound cells.

Table-2
Selected dressing materials for DFU dressings.

Sl.No	Dressing materials
1	Alginate dressing (M1)
2	Film dressings (M2)
3	Medi Foam dressings (M3)
4	Hydrogel dressings (M4)
5	Hydrocolloid dressings (M5)
6	Honey dressing (M6)
7	Beta foam dressing (M7)
8	Hydro fiber-Ag dressing (M8)
9	Low Adherent Saline dressing (M9)

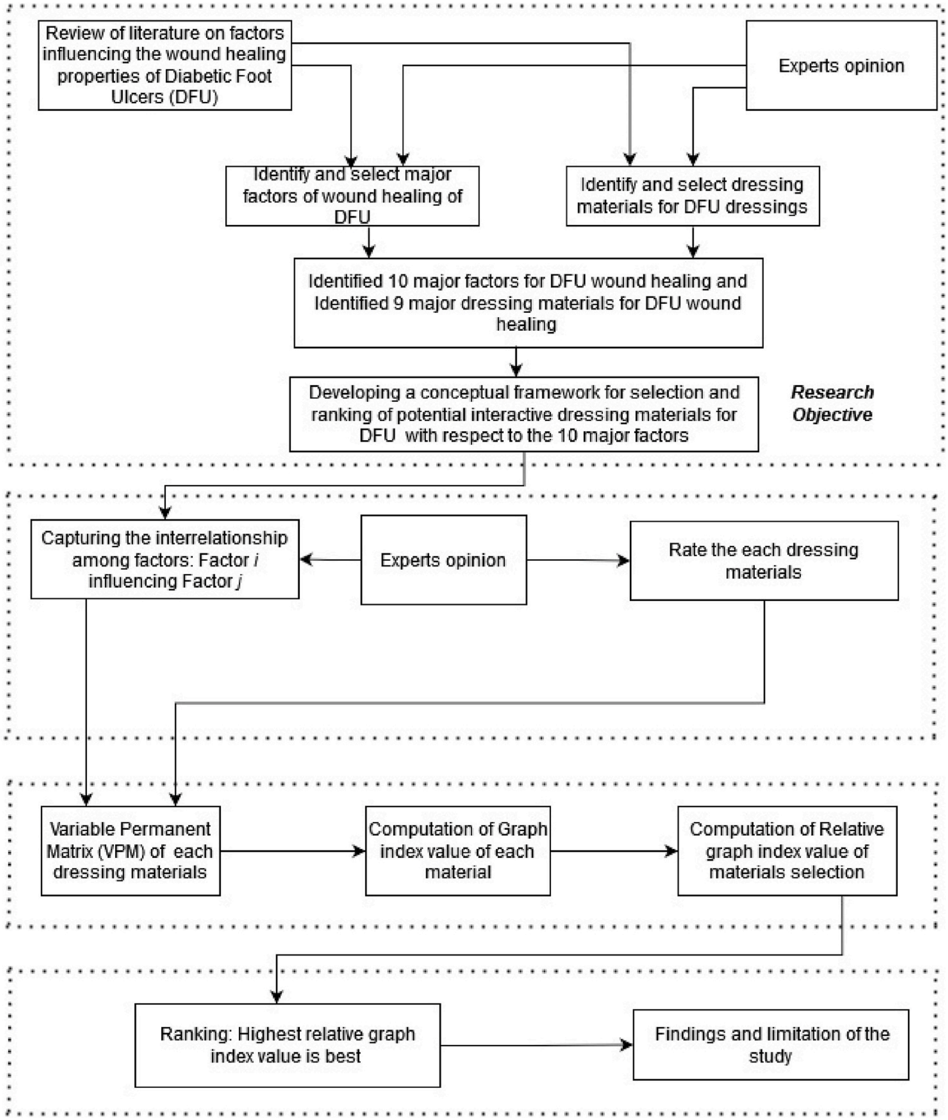

Fig. 2. Flow of selection and ranking of potential interactive dressing materials for DFU.

2.2. Graph theoretic approach

Graph theoretic (GT) approach has been widely used by various researchers in diverse fields [8,28]. For example [6], applied GT for assessment of roles of manpower in lean environment of manufacturing organization. [31] applied GT for assessment of supply chain co-ordination. [44] applied GT for assessment of transitions to flexible manufacturing systems in manufacturing organisation.

The digraph is a visual representation in a matrix form of the mechanisms and their interdependence. The matrix then converts the digraph into a mathematical form. Table 3 depicts the notations used in the graph theoretic approach. In the matrix diagonal values are rating of the concern factor in the selected dressing material. The ratings are captured from five medical doctors in India. The consensus of their opinion is taken for this selection process. In the Matrix B, B_1 represents the factor-1 presence in the concern dressing material. B_2 represents the factor-2 presence in that dressing material and so on. Table-4 represents the rating of the materials, the

Table 3
Notations.

b_{ij}	Factor *i* influencing/affecting/alter Factor *j*
B_i	Rating of factor *i*
Per B	Permanent matrix B
R	Total number of Factors

optimization direction is positive for all factors except (F3) Cytotoxic to healthy tissues influences. The optimization direction is negative for (F3) Cytotoxic to healthy tissues influences. The appropriate optimization direction is selected based on the minimum is best for negative direction and maximum is best for positive direction. The non-diagonal element of the Matrix B is the interrelationship between the factors. The $b_{1,2}$ represents the factor-1 influences in factor-2 and $b_{2,3}$ represents the factor-2 influences in factor-3 and so on. Table-5 represents the strength of the interrelationships between the factors. The strength of the interrelationships among the non-diagonal factors of the Matrix B is captured from consensus of five experts' opinion who are actively involved in biomaterials research. The permanent function is a mathematical model that helps determine the final graph index.

$$\textbf{Matrix B} = \begin{matrix} F_1 \\ F_2 \\ F_3 \\ F_4 \\ F_5 \\ F_6 \\ F_7 \\ F_8 \\ F_9 \\ F_{10} \end{matrix} \begin{bmatrix} B_1 & b_{1,2} & b_{1,3} & b_{1,4} & b_{1,5} & b_{1,6} & b_{1,7} & b_{1,8} & b_{19} & b_{1,10} \\ b_{2,1} & B_2 & b_{2,3} & b_{2,4} & b_{2,5} & b_{2,6} & b_{2,7} & b_{2,8} & b_{2,9} & b_{2,10} \\ b_{3,1} & b_{3,2} & B_3 & b_{3,4} & b_{3,5} & b_{3,6} & b_{3,7} & b_{3,8} & b_{3,9} & b_{3,10} \\ b_{4,1} & b_{4,2} & b_{4,3} & B_4 & b_{4,5} & b_{4,6} & b_{4,7} & b_{4,8} & b_{4,9} & b_{4,10} \\ b_{5,1} & b_{5,2} & b_{5,3} & b_{5,4} & B_5 & b_{5,6} & b_{5,7} & b_{5,8} & b_{5,9} & b_{5,10} \\ b_{6,1} & b_{6,2} & b_{6,3} & b_{6,4} & b_{6,5} & B_6 & b_{6,7} & b_{6,8} & b_{6,9} & b_{6,10} \\ b_{7,1} & b_{7,2} & b_{7,3} & b_{7,4} & b_{7,5} & b_{7,6} & B_7 & b_{7,8} & b_{7,9} & b_{7,10} \\ b_{8,1} & b_{8,2} & b_{8,3} & b_{8,4} & b_{8,5} & b_{8,6} & b_{8,7} & B_8 & b_{8,9} & b_{8,10} \\ b_{9,1} & b_{9,2} & b_{9,3} & b_{9,4} & b_{9,5} & b_{9,6} & b_{9,7} & b_{9,8} & B_9 & b_{9,10} \\ b_{10,1} & b_{10,2} & b_{10,3} & b_{10,4} & b_{10,5} & b_{10,6} & b_{10,7} & b_{10,8} & b_{10,9} & B_{10} \end{bmatrix}.$$

2.3. Factors' permanent matrix

After preparation of materials matrix, the permanent of a matrix given by Equation (1) is calculated; this is a multinomial function and is called permanent of B. This permanent function is a standard matrix function and is used and defined in combinatorial mathematics [10,35]. The permanent for 10 × 10 matrixes in is written as:

$$\begin{aligned} \textbf{Per B} = {} & \prod_{i=1}^{R} B_i + \sum_{i=1}^{R-1}\sum_{j=i+1}^{R}\cdots\sum_{m=q+1}^{R}\left(b_{ij}b_{ji}\right)B_kB_lB_mB_nB_oB_pB_qB_r + \sum_{i=1}^{R-2}\sum_{j=i+1}^{R-1}\sum_{k=j+1}^{R}\cdots\sum_{R=q+1}^{R}\left(b_{ij}b_{jk}b_{ki}+b_{ik}b_{kj}b_{ji}\right)\left(B_lB_nB_o\cdots B_r\right) \\ & + \left[\begin{array}{l} \sum_{i=1}^{R-3}\sum_{j=i+1}^{R}\sum_{k=i+1}^{R-1}\sum_{l=i+2}^{R}\cdots\sum_{R=q+1}^{R}\left(b_{ij}b_{ji}\right)\left(b_{kl}b_{lk}\right)B_mB_nB_o\cdots B_qB_r + \\ \sum_{i=1}^{R-3}\sum_{j=i+1}^{R-1}\sum_{k=i+1}^{R}\sum_{l=j+1}^{R}\cdots\sum_{R=q+1}^{R}\left(b_{ij}b_{jk}b_{kl}b_{li}+b_{il}b_{lk}b_{kj}b_{ji}\right)B_mB_nB_o\cdots B_qB_r \end{array}\right] \\ & + \left[\begin{array}{l} \sum_{i=1}^{R-2}\sum_{j=i+1}^{R-1}\sum_{k=j+1}^{R}\sum_{l=1}^{R-1}\sum_{m=l+1}^{R}\cdots\sum_{R=q+1}^{R}\left(b_{ij}b_{jk}b_{ki}+b_{ik}b_{kj}b_{ji}\right)\left(b_{lm}b_{ml}\right)B_nB_o\cdots B_qB_r + \\ \sum_{i=1}^{R-4}\sum_{j=i+1}^{R-1}\sum_{k=i+1}^{R}\sum_{l=i+1}^{R}\sum_{m=j+1}^{R}\cdots\sum_{R=q+1}^{R}\left(b_{ij}b_{jk}b_{kl}b_{lm}b_{mi}+b_{im}b_{ml}b_{lk}b_{kj}b_{ji}\right)B_nB_o\cdots B_qB_r \end{array}\right] \\ & + \left[\begin{array}{l} \sum_{i=1}^{R-3}\sum_{j=i+1}^{R-1}\sum_{k=i+1}^{R}\sum_{l=j+1}^{R}\sum_{m=1}^{R}\sum_{n=m+1}^{R}\cdots\sum_{R=q+1}^{R}\left(b_{ij}b_{jk}b_{kl}b_{li}+b_{ik}b_{lk}b_{kj}b_{ji}\right)\left(b_{mn}b_{nm}\right)B_o\cdots B_qB_r + \\ \sum_{i=1}^{R-5}\sum_{j=i+1}^{R-1}\sum_{k=i+1}^{R}\sum_{l=1}^{R-2}\sum_{m=l+1}^{R-1}\sum_{n=m+1}^{R}\cdots\sum_{R=q+1}^{R}\left(b_{ij}b_{jk}b_{ki}+b_{ik}b_{kj}b_{ji}\right)\left(b_{lm}b_{mn}b_{nl}+b_{\ln}b_{nm}b_{ml}\right)B_o\ldots B_qB_r + \\ \sum_{i=1}^{R-5}\sum_{j=i+1}^{R}\sum_{k=i+1}^{R-3}\sum_{l=i+2}^{R}\sum_{m=k+1}^{R-1}\sum_{n=k+2}^{R}\cdots\sum_{R=q+1}^{R}\left(b_{ij}b_{ji}\right)\left(b_{kl}b_{lk}\right)\left(b_{mn}b_{nm}\right)B_o\cdots B_qB_r + \\ \sum_{i=1}^{R-5}\sum_{j=i+1}^{R-1}\sum_{k=i+1}^{R}\sum_{l=i+1}^{R}\sum_{m=l+1}^{R}\sum_{n=j+1}^{R}\cdots\sum_{R=q+1}^{R}\left(b_{ij}b_{jk}b_{kl}b_{lm}b_{mn}b_{ni}+b_{in}b_{nm}b_{ml}b_{lk}b_{kj}b_{ji}\right)B_o\cdots B_qB_r \end{array}\right] \end{aligned} \quad (1)$$

The Variable Permanent Matrix (VPM) of dressing materials are indicating below:

Table-4
Factors rating scale of the dressing materials (diagonal factors).

Sl.No	Optimization of direction: Positive		Optimization of direction: Negative	
	Qualitative measure of factors rating in specific material	Score (B_i)	Qualitative measure of factors rating in specific material	Score (B_i)
1	Very Low (VL)	1	Extremely High (EH)	1
2	Low (L)	2	Very High (VH)	2
3	Medium (M)	3	High (H)	3
4	Good (G)	4	Good (G)	4
5	High (H)	5	Medium (M)	5
6	Very High (VH)	6	Low (L)	6
7	Extremely High (EH)	7	Very Low (VL)	7

Table-5
Inter-relationships between the factors (off diagonal factors).

Sl.No	Factor *i* influencing Factor *j*	
	Qualitative measure of interdependencies	Score ($b_{i,j}$)
1	No influence (NI)	0
2	Weakly influencing (WI)	1
3	Moderately influencing (MI)	2
4	Strongly influencing (SI)	3
5	Very strongly influencing (VSI)	4

The VPM of Alginate dressing (M1) is indicating below:

$$\text{Per M1} = \begin{bmatrix} 6 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 3 \\ 4 & 6 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 4 & 0 & 6 & 0 & 4 & 0 & 0 & 0 & 0 & 4 \\ 4 & 0 & 3 & 4 & 4 & 0 & 0 & 0 & 4 & 4 \\ 4 & 4 & 4 & 4 & 5 & 4 & 4 & 4 & 4 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 4 & 4 & 4 & 4 \\ 1 & 2 & 2 & 0 & 4 & 1 & 5 & 2 & 0 & 1 \\ 4 & 1 & 4 & 3 & 3 & 3 & 4 & 2 & 2 & 4 \\ 4 & 0 & 4 & 4 & 4 & 0 & 0 & 0 & 5 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 0 & 0 & 4 & 1 \end{bmatrix}$$

The VPM of Film dressings (M2) is indicating below:

$$\text{Per M2} = \begin{bmatrix} 3 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 3 \\ 4 & 2 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 4 & 0 & 6 & 0 & 4 & 0 & 0 & 0 & 0 & 4 \\ 4 & 0 & 3 & 5 & 4 & 0 & 0 & 0 & 4 & 4 \\ 4 & 4 & 4 & 4 & 1 & 4 & 4 & 4 & 4 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 4 & 4 & 4 & 4 \\ 1 & 2 & 2 & 0 & 4 & 1 & 4 & 2 & 0 & 1 \\ 4 & 1 & 4 & 3 & 3 & 3 & 4 & 3 & 2 & 4 \\ 4 & 0 & 4 & 4 & 4 & 0 & 0 & 0 & 2 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 0 & 0 & 4 & 1 \end{bmatrix}$$

The VPM of Medi-Foam dressings (M3) is indicating below:

$$\text{Per M3} = \begin{bmatrix} 5 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 3 \\ 4 & 7 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 4 & 0 & 6 & 0 & 4 & 0 & 0 & 0 & 0 & 4 \\ 4 & 0 & 3 & 4 & 4 & 0 & 0 & 0 & 4 & 4 \\ 4 & 4 & 4 & 4 & 6 & 4 & 4 & 4 & 4 & 4 \\ 4 & 4 & 4 & 4 & 4 & 1 & 4 & 4 & 4 & 4 \\ 1 & 2 & 2 & 0 & 4 & 1 & 5 & 2 & 0 & 1 \\ 4 & 1 & 4 & 3 & 3 & 3 & 4 & 2 & 2 & 4 \\ 4 & 0 & 4 & 4 & 4 & 0 & 0 & 0 & 2 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 0 & 0 & 4 & 1 \end{bmatrix}$$

The VPM of Hydrogel dressings (M4) is indicating below:

$$\text{Per M4} = \begin{bmatrix} 5 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 3 \\ 4 & 3 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 4 & 0 & 6 & 0 & 4 & 0 & 0 & 0 & 0 & 4 \\ 4 & 0 & 3 & 2 & 4 & 0 & 0 & 0 & 4 & 4 \\ 4 & 4 & 4 & 4 & 5 & 4 & 4 & 4 & 4 & 4 \\ 4 & 4 & 4 & 4 & 4 & 2 & 4 & 4 & 4 & 4 \\ 1 & 2 & 2 & 0 & 4 & 1 & 5 & 2 & 0 & 1 \\ 4 & 1 & 4 & 3 & 3 & 3 & 4 & 6 & 2 & 4 \\ 4 & 0 & 4 & 4 & 4 & 0 & 0 & 0 & 5 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 0 & 0 & 4 & 3 \end{bmatrix}$$

The VPM of Hydrocolloid dressings (M5) is indicating below:

$$\text{Per M5} = \begin{bmatrix} 3 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 3 \\ 4 & 2 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 4 & 0 & 6 & 0 & 4 & 0 & 0 & 0 & 0 & 4 \\ 4 & 0 & 3 & 1 & 4 & 0 & 0 & 0 & 4 & 4 \\ 4 & 4 & 4 & 4 & 5 & 4 & 4 & 4 & 4 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 4 & 4 & 4 & 4 \\ 1 & 2 & 2 & 0 & 4 & 1 & 4 & 2 & 0 & 1 \\ 4 & 1 & 4 & 3 & 3 & 3 & 4 & 4 & 2 & 4 \\ 4 & 0 & 4 & 4 & 4 & 0 & 0 & 0 & 1 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 0 & 0 & 4 & 3 \end{bmatrix}$$

The VPM of Honey dressing (M6) is indicating below:

$$\text{Per M6} = \begin{bmatrix} 7 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 3 \\ 4 & 2 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 4 & 0 & 7 & 0 & 4 & 0 & 0 & 0 & 0 & 4 \\ 4 & 0 & 3 & 5 & 4 & 0 & 0 & 0 & 4 & 4 \\ 4 & 4 & 4 & 4 & 5 & 4 & 4 & 4 & 4 & 4 \\ 4 & 4 & 4 & 4 & 4 & 1 & 4 & 4 & 4 & 4 \\ 1 & 2 & 2 & 0 & 4 & 1 & 6 & 2 & 0 & 1 \\ 4 & 1 & 4 & 3 & 3 & 3 & 4 & 3 & 2 & 4 \\ 4 & 0 & 4 & 4 & 4 & 0 & 0 & 0 & 7 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 0 & 0 & 4 & 6 \end{bmatrix}$$

The VPM of Betafoam dressing (M.
7) is indicating below:

$$\text{Per M7} = \begin{bmatrix} 2 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 3 \\ 4 & 4 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 4 & 0 & 3 & 0 & 4 & 0 & 0 & 0 & 0 & 4 \\ 4 & 0 & 3 & 6 & 4 & 0 & 0 & 0 & 4 & 4 \\ 4 & 4 & 4 & 4 & 3 & 4 & 4 & 4 & 4 & 4 \\ 4 & 4 & 4 & 4 & 4 & 1 & 4 & 4 & 4 & 4 \\ 1 & 2 & 2 & 0 & 4 & 1 & 5 & 2 & 0 & 1 \\ 4 & 1 & 4 & 3 & 3 & 3 & 4 & 2 & 2 & 4 \\ 4 & 0 & 4 & 4 & 4 & 0 & 0 & 0 & 1 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 0 & 0 & 4 & 1 \end{bmatrix}$$

The VPM of Hydro fiber-Ag dressing (M8) is indicating below:

$$\text{Per M8} = \begin{bmatrix} 5 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 3 \\ 4 & 4 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 4 & 0 & 3 & 0 & 4 & 0 & 0 & 0 & 0 & 4 \\ 4 & 0 & 3 & 7 & 4 & 0 & 0 & 0 & 4 & 4 \\ 4 & 4 & 4 & 4 & 3 & 4 & 4 & 4 & 4 & 4 \\ 4 & 4 & 4 & 4 & 4 & 5 & 4 & 4 & 4 & 4 \\ 1 & 2 & 2 & 0 & 4 & 1 & 5 & 2 & 0 & 1 \\ 4 & 1 & 4 & 3 & 3 & 3 & 4 & 2 & 2 & 4 \\ 4 & 0 & 4 & 4 & 4 & 0 & 0 & 0 & 1 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 0 & 0 & 4 & 1 \end{bmatrix}$$

The VPM of Low Adherent Saline dressing (M9) is indicating below:

$$\text{Per M9} = \begin{bmatrix} 5 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 3 \\ 4 & 7 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 4 & 0 & 7 & 0 & 4 & 0 & 0 & 0 & 0 & 4 \\ 4 & 0 & 3 & 1 & 4 & 0 & 0 & 0 & 4 & 4 \\ 4 & 4 & 4 & 4 & 7 & 4 & 4 & 4 & 4 & 4 \\ 4 & 4 & 4 & 4 & 4 & 1 & 4 & 4 & 4 & 4 \\ 1 & 2 & 2 & 0 & 4 & 1 & 7 & 2 & 0 & 1 \\ 4 & 1 & 4 & 3 & 3 & 3 & 4 & 1 & 2 & 4 \\ 4 & 0 & 4 & 4 & 4 & 0 & 0 & 0 & 2 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 0 & 0 & 4 & 1 \end{bmatrix}$$

The VPM of ideal material with respect to all factors is indicating below:

$$\text{Per Ideal Material} = \begin{bmatrix} 7 & 0 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 3 \\ 4 & 7 & 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 4 & 0 & 7 & 0 & 4 & 0 & 0 & 0 & 0 & 4 \\ 4 & 0 & 3 & 7 & 4 & 0 & 0 & 0 & 4 & 4 \\ 4 & 4 & 4 & 4 & 7 & 4 & 4 & 4 & 4 & 4 \\ 4 & 4 & 4 & 4 & 4 & 7 & 4 & 4 & 4 & 4 \\ 1 & 2 & 2 & 0 & 4 & 1 & 7 & 2 & 0 & 1 \\ 4 & 1 & 4 & 3 & 3 & 3 & 4 & 7 & 2 & 4 \\ 4 & 0 & 4 & 4 & 4 & 0 & 0 & 0 & 7 & 4 \\ 4 & 4 & 4 & 4 & 4 & 3 & 0 & 0 & 4 & 7 \end{bmatrix}$$

3. Results

The results showed (Table 6) that the graph index ideal material value is 34511876853 for selection of suitable material. The ranking of relative index value of materials selection may be relatively made using the ideal value.

Relative graph index value of materials selection = Graph index value of material *i / Index ideal value*

3.1. Interpretation of the permanent matrix and graph index values

Among the nine wound dressing materials selected, Alginate dressings secured a high relative graph index value of 0.934889, being the best quality dressing material among the materials concerned. As per the expert's rating, the Alginate dressing material possess excellent wound healing, anti-inflammatory and absorbent properties making it well accepted by the patients, but limited capacity to either regenerate the wound or to be used as a drug delivery system to deliver regenerative drugs to the wound site.

Honey Dressing was the second-best material by analyzing the various wound healing properties studied mathematically whose relative graph index value was appeared to be 0.92752. As per the expert's rating, Honey dressings have high patient preference as it helps to regenerate the deep tissues of the wound by reducing inflammation and by providing antimicrobial protection. But, the major disadvantage of honey is that additional dressings need to be used for exudate balance while using honey dressing and this will not be a good drug carrier to load wound healing materials to be delivered to the wound site.

Medifoam dressings with 0.923147 relative graph index value appeared on third position as per the calculation which is a popular choice among patients with heavy exudates providing excellent mechanical protection to the wound according to expert's opinion. This is very convenient for wounds of any shape including bony prominences as it provides good mechanical protection but the disadvantage lies in its required frequent dressing changes. This is one way good in managing wound exudates, but repeated dressing changes may affect the newly formed epithelial cover and delay wound healing and this can also never be considered as a wound regenerative drug delivery material.

Saline dressing with a relative graph index value 0.921321 was in fourth positions. Wet-to-dry dressings are a means of mechanical debridement which is very absorptive as well as adherent and one of the cheapest dressings used throughout the world, but requires frequent dressing changes (twice or thrice a day based on wound severity) which may affect the re-epithelialization of the wound making it a low accepted dressing material by patients.

Hydrogel Dressings with relative graph index value 0.916918 came in the fifth position according to the calculations and expert's opinion, even though it has excellent wound healing, anti-inflammatory and exudate control properties and one of the cheapest wound dressings for DFU. The major limitation of hydrogel dressings is its poor antimicrobial property and low wound regenerative property but hydrogels are excellent material for any kind of drug delivery, including antimicrobial, angiogenic or regenerative drugs making it a promising candidate to be used as an interactive dressing material.

All other dressing materials of the study had low preferences due to various limitations which largely contribute to the slow healing of a diabetic foot ulcer. The results were linear to the mode of the general opinion of podiatricians and diabeticians.

Table 6
Results of the graph index.

Dressing material	Graph Index (Permanent value)	Log_{10}	Relative graph index value of materials selection	Rank
Alginate dressing (M1)	7109314272	9.851828	0.934889	1
Film dressings (M2)	2234528128	9.349186	0.887191	7
Medi Foam dressings (M3)	5346770336	9.728092	0.923147	3
Hydrogel dressings (M4)	4596811056	9.662457	0.916918	**5**
Hydrocolloid dressings (M5)	1748364784	9.242632	0.877079	9
Honey dressing (M6)	5945324864	9.774176	0.92752	2
Beta foam dressing (M7)	2055845168	9.31299	0.883756	8
Hydro fiber-Ag dressing (M8)	3540439460	9.549057	0.906157	6
Low Adherent Saline dressing (M9)	5115059858	9.708851	0.921321	4
Index Ideal value (Ideal material with respect to all factors)	34511876853	10.53797	1	

4. Discussion

The effective management of a DFU includes both wound dressing as well as systemic and topical wound regenerative therapy. The development of a successful topical treatment for leg ulcers are a challenge for the scientific community. There are several modern scientific achievements contributed to the effective regeneration of wounds in DFU, but the high cost of growth factor and allied regenerative therapy make it less accessible to the middle and poor class people to such promising therapeutic measures. Recent innovations incorporating growth factors, stem cells and therapeutical agents in natural and synthetic matrices, coupled with routine dressings are found to be very beneficial in regenerating diabetic foot ulcers while effectively managing the exudate and microbial control.

The paper was attempting to find a 'functional' wound dressing material or 'an interactive dressing material 'providing natural wound healing properties, and wound protection along with an additional advantage of being used as a drug carrier for slow and consistent release of regenerative drugs. A cost-effective dressing material of high wound healing property incorporated with growth stimulating regenerative drugs will be a popular next generation treatment option for diabetic foot ulcer, providing the benefits of growth factor therapy as well as dressing effect; and will be of patient acceptance, especially if the material doesn't demand repeated dressing changes and is of low cost.

The selection of a suitable dressing material depends on various factors [33]. Some dressing materials are good in some factors responsible for a better healing at the same time, their limitations may make them less preferable at times [15,52]. Being a highly resistant wound, DFU need a proper guided protocol-based treatment strategy and the selection of a proper dressing material according to the nature of wound is of prime importance which was made easy by the current predictive calculations using graph theoretical approach.

As per the calculations, the first four materials listed as priority materials (Alginate, Honey, Medifoam and Saline Dressings) were good performers in providing mechanical protection, exudate management and in terms of cost effectiveness. Even though these dressings are of popular choice mainly because of their cheap cost, they neither exhibit an inherent wound regenerative potential nor can be used as an effective drug delivery system which can hold and release functional regenerative drugs or antimicrobial drugs to the degenerating diabetic wound environment.

Hydrogels which came in the fifth position as per the graph index value-based ranking, is having several high performing attributes for chronic wound healing [42]. Hydrogels are attractive materials for chronic wound dressing as they provide moist environment for the wound bed and can provide a 3D skin-like mechanical properties which can deliver wound regenerative and antimicrobial drugs for adequate wound repair [24]. Hydrogels hydrates dry necrotic and slough wounds, provides an analgesic effect promoting autolysis and are the best choice for the treatment of dry wounds with necrotic eschar [23]. They debride the wound by rehydrating up to a 50% debridement level more quickly than wet-to-dry dressings and are more cost-effective [20].

This finding is also supported by recent clinical research observations *in vivo* [25, 49].

There are several low-cost natural hydrogels of biological origin like silk Sericin protein and collagen, which are used for drug delivery [1,39]. Some of them were widely used as wound healing gels in ancient times, but the limitation of hydrogels is their poor antimicrobial property which push them aside from being considered as a good diabetic dressing material. Natural polymers such as chitosan, silk sericin, alginate, and gelatin can improve diabetic wound environment, having the advantage of biocompatibility, bioactivity, biodegradability, and antibacterial properties [13]. Even then semi-synthetic hydrogels are under development, which can incorporate multiple drugs in combination and can provide selective, prioritized, and controlled release of the drugs to the wound site at various time points as the healing and regeneration of the wound progresses [19].

Modified hydrogels carrying regenerative drugs and antimicrobial drugs can be developed which can effectively regenerate the diabetic foot as well as providing protection and exudate control of the wound without compromising antimicrobial property, points out the utility of hydrogel matrix as carriers of regenerative drugs with sustained release of the active drug in a hydrogel matrix. Recent advancements in diabetic ulcer research have developed several natural and synthetic polymers for composite hydrogel dressings delivering bioactive agents like, platelet rich plasma, antioxidants, stem cells, growth factors, and insulin, among others [24].

To summarise, 'functional hydrogels' can be proposed as a promising novel dressing material for DFU and it has the potential to become the most attractive and acceptable 'Interactive wound dressing system' in the field of wound dressing material in recent decades offering single to multiple functions.

5. Conclusion

The paper was attempting to select an ideal, interactive, 'functional wound dressing material' which can heal the wound, manage exudates as well as effectively deliver regenerative drugs to the wound site for Diabetic foot ulcer treatment. For the purpose, nine conventional dressing materials of popular choice were selected and studied for a comparative assessment for ten cardinal factors influencing chronic wound healing and regeneration. An assessment framework has been developed to rank the selected materials using 'Graph theoretic approach' for the purpose of identifying the best material having good wound healing and regenerative properties. The material should also be used for interactive drug delivery for the slow and consistent release of antimicrobial, angiogenic and wound regenerative drugs to the deep tissues of chronic wounds like DFU. Based on the graph index values, Alginate, Honey, Medifoam, Saline, and Hydrogel dressings secured the top five ranks considering all ten factors selected for the study. But among the top five materials, the only material which can be used as a drug delivery system is the hydrogel dressing. Moreover, the recent scientific data in the field of *in vivo* experimentations supports the author's finding, which indicate that the development of 'multifunctional hydrogel dressings' like 3D polymeric systems, natural or semi synthetic, provide bioactivity to stimulate desired cell infiltration and proliferation in chronic diabetic foot ulcers [24].

The emerging biomedical advancements have been selecting hydrogels as a revolutionary biomaterial for tissue engineering and tissue repairing processes and also several natural polymers are used as non-immunogenic, biodegradable injectable drug delivery agents in cancer immunotherapy [38,50]. Moreover, hydrogels can be easily functionalized, modified, and can be used in several physical forms [32], making it an exceptional futuristic drug delivery system for tissue regeneration and chronic wound management.

The proposed framework can be modified and applied in various contexts, with different materials and decision-making properties for any kind of bio-medical applications related to material or drug selection. Even then, the study is only a 'preliminary predictive assessment' based on expert's opinion and ranking by applying graph theoretic approach, and further studies, either clinical or *in vivo* studies need to be followed for a conclusive remark regarding material selection.

Author contribution statement

Lakshmi Priyadarsini: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Data collection; Wrote the paper.

Suresh: Performed the experiments; Analyzed and interpreted the data; Contributed to methodology; Analysis tools or data.

Nikhila: Data collection; Performed the experiments, Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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