

# GLOBAL JOURNAL

OF MEDICAL RESEARCH: I

## Surgeries and Cardiovascular System

Delivery of Nebivolol Hydrochloride

A Patient with Enlarged Left Atrium

### Highlights

Development of Elastic Nanovesicles

Interchangeable Prosthetic Heart Valve

Discovering Thoughts, Inventing Future



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SURGERIES AND CARDIOVASCULAR SYSTEM

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## Esophageal-Pleural Fistula after Intraoperative Transoesophageal Echocardiography in a Patient with Enlarged Left Atrium

By Mario Torre, MD, MSc, Maria Giovanna Vassallo, MD, Maria Grazia Romeo MD, Alberto Bonadies, MD, Antonio Longobardi, MD, Francesco Pirozzi, MD, Pompea Bottiglieri, MD, Annarita Iavazzo, MD, Leonardo De Luca, MD & Enrico Coscioni, MD

**Abstract-** After mitral valve replacement in an 81-year-old woman, there was evidence of an important communication between the esophagus and the right pleura. Diagnosis was confirmed with Oral Gastrografen radiography and esophagoscopy. Thoracic computed tomography scans better indicated fistula location and extension, but also showed the close relationship and the compression of huge left atrium on the oesophagus. Our hypothesis was that the lesion was induced by transoesophageal echocardiography probe in a favourable setting. An enlarged left atrium should be recognized as a risk factor for TEE-induced esophageal perforation, especially in fragile patients, with marked esophagus distortion.

**Keywords:** *esophageal fistula, pleural fistula, transoesophageal echocardiography, left atrium, esophageal perforation, case report.*

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# Esophageal-Pleural Fistula after Intraoperative Transoesophageal Echocardiography in a Patient with Enlarged Left Atrium

Mario Torre, MD, MSc<sup>α</sup>, Maria Giovanna Vassallo, MD<sup>σ</sup>, Maria Grazia Romeo MD<sup>ρ</sup>, Alberto Bonadies, MD<sup>ω</sup>, Antonio Longobardi, MD<sup>¥</sup>, Francesco Pirozzi, MD<sup>§</sup>, Pompea Bottiglieri, MD<sup>χ</sup>, Annarita Iavazzo, MD<sup>ν</sup>, Leonardo De Luca, MD<sup>θ</sup> & Enrico Coscioni, MD<sup>ζ</sup>

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**Keywords:** esophageal fistula, pleural fistula, transoesophageal echocardiography, left atrium, esophageal perforation, case report.

## I. CASE PRESENTATION

An 81-year-old woman was admitted to our cardiac surgery department because of a severe dyspnoea of one month duration also at rest and an episode of acute pulmonary oedema. At the admission she had mild dyspnoea, a blood pressure of 110/70 mmHg and a long standing persistent atrial fibrillation rhythm at the electrocardiogram. Blood test were almost normal: haemoglobin 13.2 g/dl, transaminases < 20 mg/dl, creatinine 0.83 mg/dl, brain natriuretic peptide 657 pg/ml. Chest radiograph indicated a significant increase of the vascular network in both the lungs. Transthoracic echocardiography showed a normal left ventricular systolic function, with a 52% ejection fraction, a moderately dilated left ventricle (tele-diastolic volume: 89 ml/m<sup>2</sup>), and a huge left atrial chamber (area: 48 cm<sup>2</sup>, volume/BSA: 52 ml/m<sup>2</sup>). At the doppler examination, a severe and symptomatic mitral valve regurgitation was diagnosed (vena contracta: 7

mm, EROA 46 mm<sup>2</sup>, regurgitant volume: 72 ml). The aortic valve appeared to be normal and there was a minimal physiologic tricuspid regurgitation. The heart team opted for a surgical approach and then she underwent mitral valve replacement and a porcine bioprosthesis (Carpentier Edwards Perimount Magna Mitral Ease, 29 mm) was implanted. Transoesophageal echocardiography (TEE) was used in a conventional intraoperative setting (at baseline, for de-airing and surgical result evaluation) and the probe was inserted without any resistance. On the fourth postoperative day, there was evidence of a yellowish material from the right thoracic drainage, while she was drinking. She was asymptomatic, afebrile, with modest leucocytosis and increase of inflammatory indexes.

Suspecting the existence of an esophageal-pleural fistula, Methylene blue was given orally, and it coloured the chest tube drainage. Parenteral nutrition was started immediately. Antibiotic prophylaxis was then started and medications were given intravenously.

Oral Gastrografin radiography confirmed a communication between the esophagus and the right pleura (Fig. 1).

Thoracic computed tomography (CT) scans clearly indicated the fistula location (Fig. 2A) and esophagoscopy showed a wide opening –6cm – on the right surface of the distal esophagus (Fig. 2B). No other anomalies were found. We speculated that perforation could be due to ischemia of the esophagus resulting from the combination of TEE probe compression and non-pulsatile flow during a lengthy on pump procedure, in a fragile patient, as it is already well reported in the literature<sup>1</sup>. Moreover, in our patient, CT images clearly showed a giant left atrium – indexed volume 52 ml/m<sup>2</sup> – compressing and displacing the oesophagus, right in the fistulated region. Several studies reported cases of esophagus compression and distortion by enlarged left atrium related to mitral valve disease<sup>2</sup>: this anatomic feature should be recognized as a risk factor for TEE-related esophageal complications.

Finally, a 15 x 2 cm auto expandable esophageal stent was placed endoscopically. No

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residual communication was observed, and a new CTscan confirmed the good result (Fig.3).

## II. DISCUSSION

TEE is used routinely during cardiac surgery to monitor cardiac haemodynamic, weaning off cardiopulmonary bypass, air removal, and valve function, butal though it is a relatively safe exam, it may result in some complications<sup>3</sup>. During cardiac surgery, the insertion, manipulation, and removal of the probe may increase those complications<sup>4</sup>. Moreover, when cardiopulmonary bypass (CBP) is necessary as in this case, patient's temperature is lowered to 32-29° C, there is a significant inflammation reaction and the blood flow provided has a continuous pattern, not a pulsatile one. All these conditions can cause micro-ischemia, facilitate tissue damage and weak the oesophageal wall, even if any movement or manipulation of the probe was gentle and TEE examination was discontinued intermittently and automatically to decrease the probe temperature and the risk of tissue damage. In addition, a huge left atrium might chronically compress the anterior oesophageal wall, causing local ischemia, and might displace it, generating dangerous bends which can make easier a TEE-mediated damage. However it has been reported that the majority of iatrogenic esophageal damages occurs in patients with an unknown esophageal or gastric pathology<sup>5</sup>.

In this case, our hypothesis was that the lesion was induced by transoesophageal echocardiography probe in a favourable setting: huge left atrium which displaced the thoracic oesophagus, in a very frail patient who underwent a quite long surgical procedure, using CBP with long-time perfusion with continuous blood flow.

## III. CONCLUSION

TEE is a fundamental tools during cardiac surgery, however for patient safety, comprehensive intraoperative TEE guidelines should always be followed. And an enlarged left atrium should be recognized as a main risk factor for TEE-induced esophageal perforation, especially in fragile patients, with marked esophagus distortion.

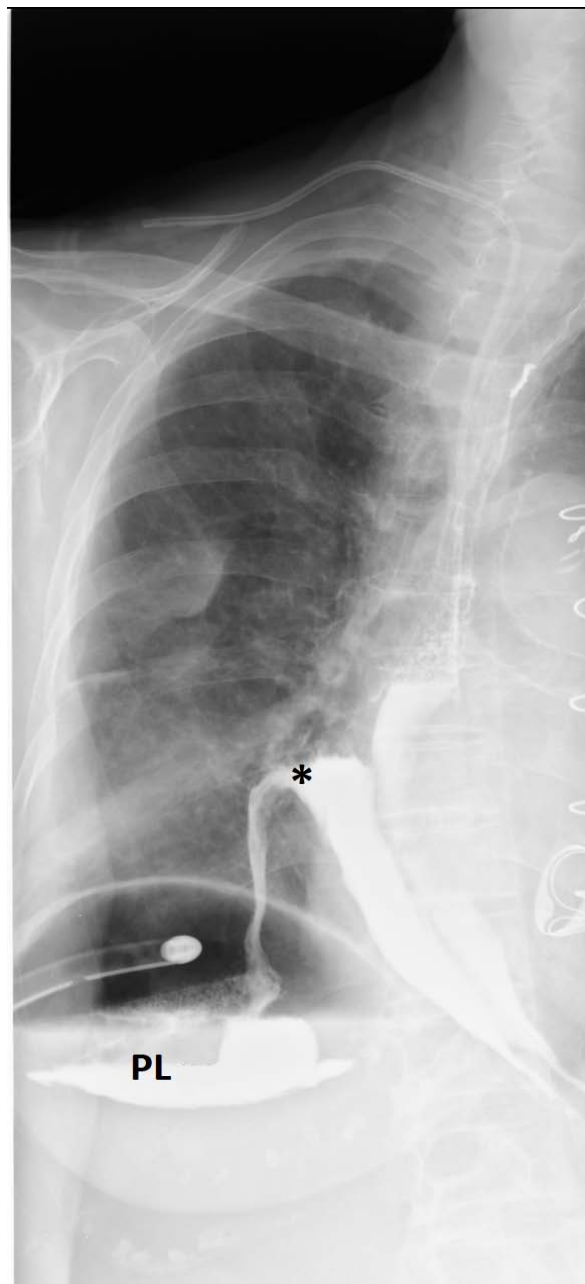
The authors have no conflict of interest to declare and no founding.

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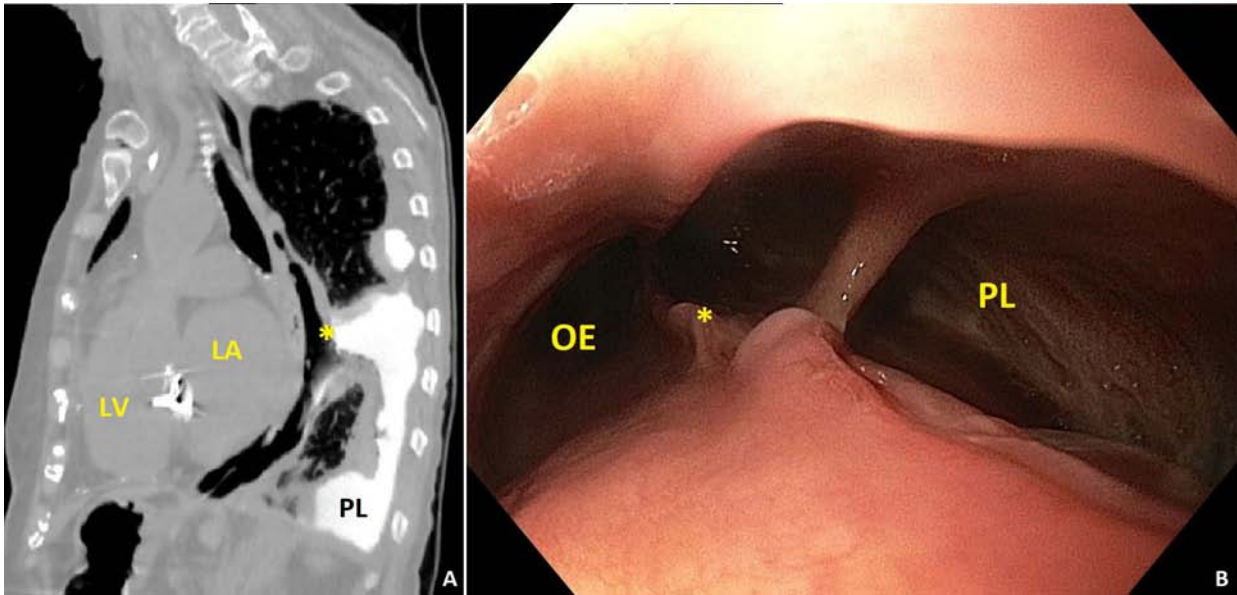
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*Fig. 1:* The asterix shows the communication between the esophagus and the right pleura at the oral Gastrografin radiography. PL: Right Pleura.





*Fig. 2 A:* Computed tomography scan displayed pleural-esophageal fistula (indicated by the asterisk) with contrast effusion in the right pleura, the enlarged left atrium and its distortion of the oesophagus, at the level of the lesion. LA: Left Atrium; LV: Left Ventricle; PL: Right Pleura. B - Esophagoscopy showed the level and the extension of the fistula (indicated by the asterisk) on the right surface of the distal oesophagus, for the subsequent stenting procedure. OE: Oesophagus; PL: Right Pleura.



*Fig. 3:* Final computed tomography evaluation of stent deployment in the oesophagus (asterisk) with no residual communication. LA: Left Atrium; LV: Left Ventricle.



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## Eight Types of Interchangeable Prosthetic Heart Valve: A Mini Review

By Roberto de Menezes Lyra, M.D., M.Sc.

**Abstract- Introduction:** Bioprostheses are prone to structural degeneration and have limited durability. Implantation of a prosthetic heart valve is risky when subsequent reoperation is required to replace the worn prosthetic valve.

**Methods:** A review of interchangeable prosthetic heart valve models between 1984 and 2022.

**Results:** Eight types of bioprostheses with interchangeable mechanisms, intended for heart valve prosthesis implantation and rapid substitutions during reoperations, aim to describe their framework's mechanical structure and increase knowledge of their coupling mechanisms. These are intended to reduce the surgical risks associated with the excision of the old, worn bioprosthesis and shorten the reoperation time.

**Conclusion:** These new experimental paradigms should prove the operability of the removal mechanism of all types of interchangeable bioprostheses and the effectiveness of the new quick connector and its perfect locking parts during heart valve reoperation, which should facilitate the reoperation operation, faster and safer.

**Keywords:** heart valve diseases, heart valve prosthesis implantation, biological heart valve, bioprosthesis, reoperation.

**GJMR-I Classification:** DDC Code: 621.84 LCC Code: TJ223.V3



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**Keywords:** heart valve diseases, heart valve prosthesis implantation, biological heart valve, bioprosthesis, reoperation.

## I. INTRODUCTION

Since 1968, the introduction of biological heart valves has involved a tremendous amount of work and research that has utilized effective valve replacement therapy to treat valvular heart disease.<sup>(1)</sup>

The future of heart valve treatments discusses improving valve structure and degradation of bioprostheses and compares pericardial heart valves to porcine valves.

In addition, implantation of a prosthetic heart valve (PHV) can be considered a risky surgery and may aggravate if subsequent reoperation is required to replace the worn prosthetic valve.

This mechanical bioengineering approach encompasses the coupling and uncoupling mechanisms of their components.

## II. METHODS

Relevant literature databases on eight types of i-BHVs were searched on PubMed and MEDLINE from 1984 to 2022.

Martin J.R. et al. (1984) developed the first i-BHV, which consisted of three parts: the sewing ring, the i-BHV, and the retaining ring. The sewing ring mounts onto the high-profile support ring, which has an internal stop for docking with the i-BHV support structure and an inner channel for attaching the retaining ring. The support framework for the i-BHV has on its underside a small flap that forms a step protruding from the outside, intended to track the inner circular stop of the ring that supports the sewing ring. They implanted the prototype in the tricuspid position. At the follow-up operation, which took place after eight months, the valve was changed in 8 minutes. The ring supporting the sewing ring in situ facilitated the procedure. They reported no thrombotic phenomena or periprosthetic leaks. The wound healed, and growth of fibrotic pannus and underlying tissue less than 1 mm thick was found. Finally, the authors propose another new project to optimize the reduction of the effective valve area of this model.<sup>(2)</sup>

Fernandez J et al. (1987) described the Tasconbioprostheses, consisting of the sewing ring and the i-BHV. The plastic material screw locking mechanism was used for the coupling and engagement between the sewing ring and the support framework for the porcine bioprostheses. It reported implant safety in 25 patients and satisfactory short-term hemodynamic properties. However, the fibrous tissue blocked the screw thread in the longterm, making it difficult to separate the parts and safely remove the i-BHV.<sup>(3)</sup>

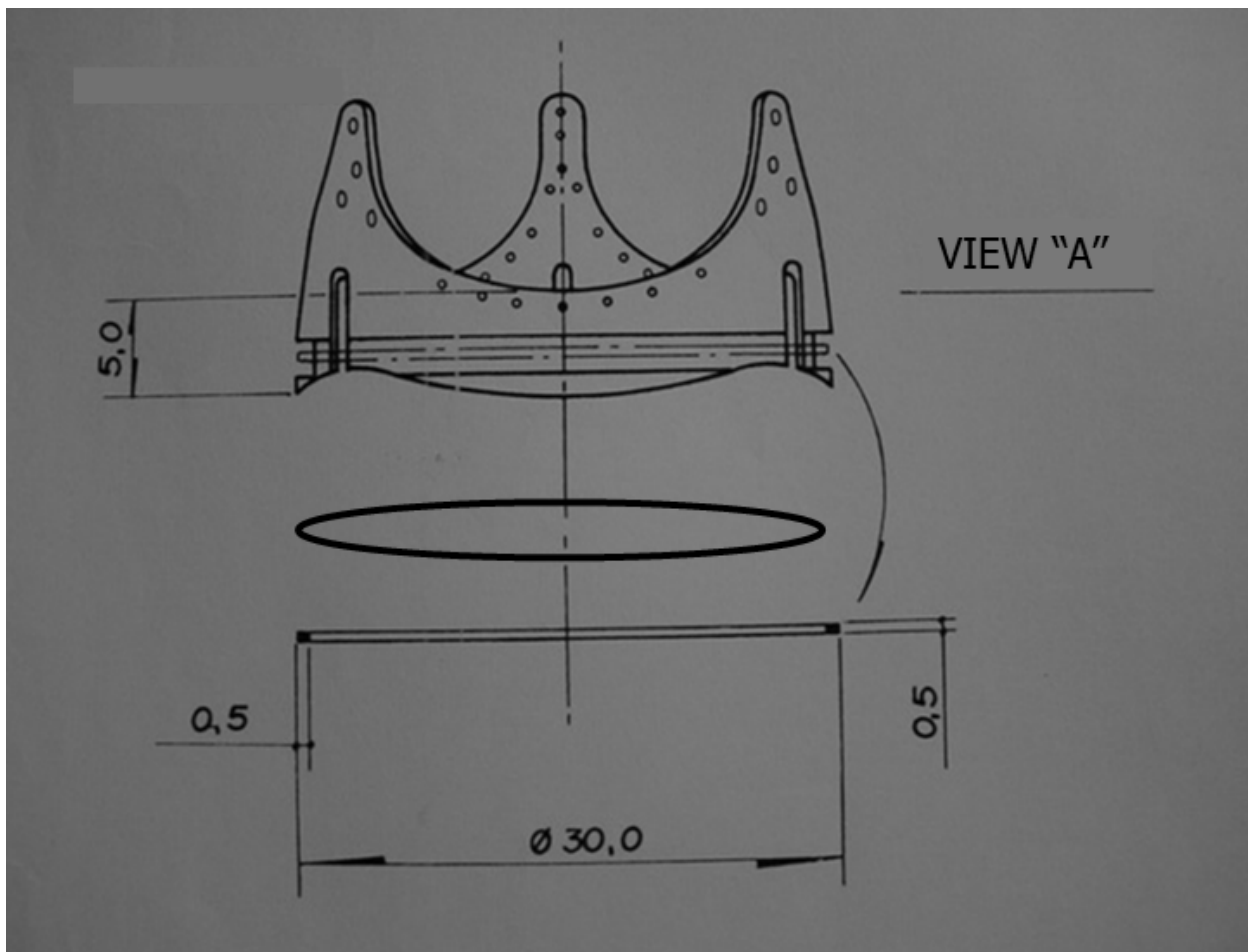
Cooper DK et al. (1988) used a Bjork-Shiley mechanical valve prosthesis as an interchangeable model. He mentioned that this interchangeable coupling mechanism could also be used for bioprostheses. The project consists of two parts: the sewing ring and the i-BHV. The engagement and disengagement between the parts are possible thanks to the spring-mechanical property of the steel half-ring covered by the sewing ring. The half-ring is made of malleable stainless-steel wire in the form of a self-locking type semi-circular clamp. Each end of the half ring is shaped like two small rings visible and accessible from outside the sewing ring. Tweezers with hooked ends were developed for these rings. When activated, it increases the circumferential diameter of the half-ring by a few millimeters; when the pressure is removed, the ring returns to its original diameter at rest. At rest, the half-ring has a diameter that encompasses the outer groove

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of the i-BHV in a circle way. Enlarging with the forceps allows insertion to dock the new i-BHV and its removal. In vivo tests were carried out on ten baboons.<sup>(4)</sup>

Lyra et al. (1992) developed an i-BHV consisting of the metal ring that supports the sewing ring and the

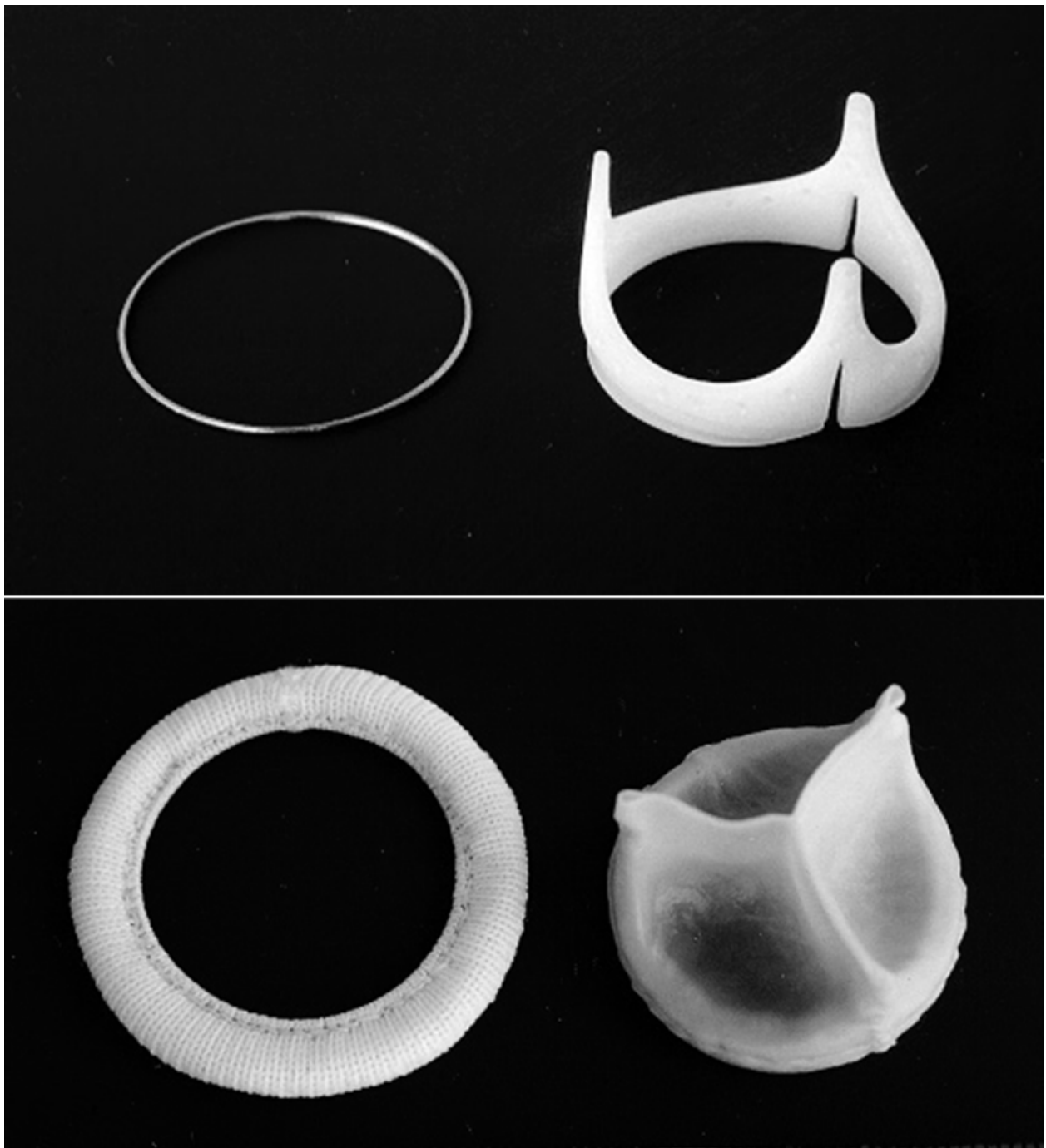
coiled framework made of a flexible plastic structure with spring properties (*Figure 1*).



*Figure 1:* VIEW "A": drawing in millimeters of the sinuous support for the bioprosthesis with the interchangeable framework in the front view and the ring that holds the sewing ring in the oblique view and the front view.

The bioprosthetic framework has a sinuous and circular shape that gives it malleability and behaves with the mechanical properties of a spring. As a result, this penetrates with its underside framework during its circular compression, then relaxes again and snaps into engagement with the sewing ring (*Figure 2*).





**Figure 2:** Interchangeable Bioprosthetic Heart Valve =i-BHV. Photographs view of the i-BHV separated from its sewing ring. The top left photo is the stainless-steel framework, one of which is used to make the sewing ring to support it and cover it with mesh, as shown below. Above right, the framework of the i-BHV is made of flexible plastic polymer and covered with bovine pericardium. This mechanism aids in the assembly of the bioprostheses, as shown below.

The i-BHV separation can be achieved by breaking the framework at its three posts with laminectomy surgical forceps, allowing decoupling with the sewing ring. The i-BHV model was tested in a pulsed pneumatic ventricle simulator and behaved like ordinary bioprostheses. No animal testing was performed.<sup>(5)</sup>

Jansen et al. (1992), this model consists of its sewing ring and the i-BHV. A metallic ring made from a

metallic nickel-titanium alloy (nitinol) was incorporated into his sewing ring. This metal alloy with plastic properties allows its diameter to change significantly when subjected to a temperature variation between 20 and 37 degrees Celsius and has excellent temperature-induced conformation and memory properties, with the ability to regain its predetermined shape. This diameter variation enabled the coupling mechanism around the

external channel of the i-BHV support framework obtained through the thermal contraction of the metal ring of the sewing ring. Its detachment occurs with an increase in temperature, which expands the diameter of the metal ring, making it possible to detach the i-BHV from the metal ring of the sewing ring. There are no animal studies in the literature.<sup>(6)</sup>

Fukamachi et al. (2008) proposed an i-BHV consisting of the sewing ring and the i-BHV. The researchers incorporated a magnetic metal ring into the sewing ring and another into the support framework of the i-BHV. The model used the magnetic attraction between two magnetic rings to couple and lock between the parts. The prototype met the target in vitro tests and withstood the separation force in a pulsating pneumatic ventricle simulator. In vivo testing demonstrated the hemodynamic effects of i-BHV in acute experiments on three sheep. All experiments efficiently performed both fixing and loosening between the magnetic pieces using forceps specially designed to break the magnetic attraction between the components. The next i-BHV was magnetically coupled to the sewing ring to simulate re-exchange during reoperations.<sup>(7)</sup>

Ebner et al. (2012) proposed an i-BHV that consists of two parts: the sewing ring and the i-BHV. Both frameworks were made of plastic material, giving them enough malleability to allow for the mechanical coupling between the parts. The shape of the ring that supports the sewing ring went through modifications, and its framework has three ascending bars with hooks at the ends designed to couple to the i-BHV's support framework. The i-BHV's support structure is sinuous and circular. And it has three horizontal bars added to its three ascending bars, where there is a quick coupling mechanism between the two parts. The three hook bars at the ends of the ring that supports the sewing ring penetrate the interior of the i-BHV's sinuous support framework and are connected to its three horizontal bars by quick-connect couplings. Therefore, the coupling between the pieces takes place at these three points. The forced engagement between the parts is only possible due to the deformability of the plastic material of the two parts. The three struts of the top can be compressed internally while the tortuous support structure of the bioprosthesis expands. After the coupling hooks pass the horizontal bars of the i-BHV support framework, the two parts lock and return to their rest positions. In three patients, the i-BHV set behaved like conventional bioprostheses. Performance was excellent, and it was easy to insert the first surgical implant. The coupling lasted 3 to 6 minutes intraoperatively.<sup>(8)</sup>

Eren et al. (2022) described a novel transcatheter aortic valve implantation (TAVI) with a valve system consisting of two components: A retention device that could be surgically implanted or attached to a catheter and a novel valve system called

exchangeable-TAVI (e-TAVI). To facilitate the minimally invasive removal and replacement of an e-TAVI, a novel e-TAVI electromagnetic vascular catheter was developed to remove and retrieve a failed e-TAVI, followed by the immediate placement of a new valve. The experimental research revealed the need to define new bond-coupling constraints between the electromagnets and the ferromagnets in the cladding simulations, suggesting that another physical coupling mechanism is required to realize the e-TAVI concept. Moreover, the attachment between the catheter and the e-TAVI framework should be tight enough to allow its removal through the catheter pathway.<sup>(9)</sup>

### III. DISCUSSION

The innovative i-BHV is ahead of its similar, not interchangeable, not enhancing its durability or performance, but rather the ease and the security of detaching and then replacing it with the next i-BHV when reinserted in the next operation.

Therefore, the perspectives and limitations of these reviews, with multicenter publications and a small number of cited surgeries, make it difficult to generalize the results.

The engagement and decoupling between parts are possible thanks to these innovations. Fukamachiet al.<sup>(7)</sup> report the desirable advantages of an i-BHV, such as:

1. Simple surgical fixation of the sewing ring together or not with the i-BHV.
2. Reduction of operational risks related to removing the bioprosthesis's old, worn-out sewing ring.
3. Ease and safety in removing the i-BHV during reoperation.
4. Hermetic sealing between parts.
5. No growth of fibrotic tissue at the internal junction interface between the pieces.
6. The optimized lumen-to-ring ratio is to obtain the largest possible area of the valve opening, despite the addition of the coupling mechanism between the parts.
7. The sewing ring frameworks and the framework that stents the valve prosthesis leaflets must be made of medical grade material, malleable, and fatigue resistant.
8. Durability and security of the coupling and locking mechanism between the parts.
9. Absence of long-term fragility or mechanical stress fractures due to structural changes in the bioprosthesis support framework and sewing ring.

Due to the degeneration of bioprosthetic heart valves, the interchangeable bioprosthetic heart valve (i-BHV) describes new paradigms based on the innovative hypothesis of heart valve surgery to improve reoperations, supposedly making them safer and faster.<sup>(10)</sup>



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# Development of Elastic Nanovesicles for Enhanced Transdermal Delivery of Nebivolol Hydrochloride

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**Abstract-** The present investigation is to prepare and evaluate transdermal Nebivolol hydrochloride transdermal patches. Rotary evaporation process was used to prepare the nanocarriers. Soya lecithin when used in conjunction with Labrosol was proven to be an effective edge activator for the manufacture of Nebivolol hydrochloride nanocarriers. Several characteristics of the produced nanocarriers were measured, including size, entrapment efficiency, Zeta potential, and photodynamic interference. A design expert programme called DOE (central composite design) was used to optimise the formulations that were chosen. The improved formulation (40% w/v Labrosol and 68% w/v soya lecithin) exhibited particle sizes of 1434.5nm, Zeta value of -39.8, and a percent Entrapment effectiveness of 96 percent, among other characteristics.

**Keywords:** *transfersomes, transdermal, nebivolol hydrochloride, transfersomal patches, edge activators, soya lecithin.*

**GJMR-I Classification:** *NLMC Code: QV 38*



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# Development of Elastic Nanovesicles for Enhanced Transdermal Delivery of Nebivolol Hydrochloride

Aparanjitha. R<sup>α</sup>, Sunitha Reddy. M<sup>σ</sup> & Sarangapani. M<sup>ρ</sup>

**Abstract-** The present investigation is to prepare and evaluate transdermal Nebivolol hydrochloride transdermal patches. Rotary evaporation process was used to prepare the nanocarriers. Soya lecithin when used in conjunction with Labrosol was proven to be an effective edge activator for the manufacture of Nebivolol hydrochloride nanocarriers. Several characteristics of the produced nanocarriers were measured, including size, entrapment efficiency, Zeta potential, and photodynamic interference. A design expert programme called DOE (central composite design) was used to optimise the formulations that were chosen. The improved formulation (40% w/v Labrosol and 68% w/v soya lecithin) exhibited particle sizes of 1434.5nm, Zeta value of -39.8, and a percent Entrapment effectiveness of 96 percent, among other characteristics.

The optimised formulation was combined into transdermal patches utilising various concentrations of HPMC E5 and HPMC E15, as well as the plasticizer PEG-400. The skin permeation investigations of the optimal transdermal patch (HPMC E5 3% v/v, 1.5% v/v PEG-400, and 2% nano suspension, i.e., 40% v/v Labrosol and 68% soya lecithin) have flux of 43 (g/cm<sup>2</sup>/hr), permeation coefficient of 14.5 (cm/hr) (K<sub>px</sub>103), enhancement ratio of 2.8, lag time of 0.2 The optimised patches have non-fickian diffusion in the Korsmeyer-Peppas model with n value 0.8 and zero order kinetic type of drug release. In vitro drug release tests, skin permeation studies, and other tests were performed on the patches. The findings of the in vitro assays show that the manufactured patches had improved drug release rates when compared to standard transdermal patches.

**Keywords:** *transfersomes, transdermal, nebivolol hydrochloride, transfersomal patches, edge activators, soya lecithin.*

## I. INTRODUCTION

Transdermal administration is acknowledged as a promising approach for local and systemic medication delivery. Transdermal medication delivery avoids hepatic first pass metabolism and enhances patient compliance. However, the stratum corneum's highly structured structure acts as a barrier to drug permeability and must be changed to give poorly

penetrating medicines<sup>[1]</sup>. The use of chemical penetration enhancers would greatly increase the number of transdermal medication molecules.

In Saudi Arabia, where it affects about one-quarter of the adult population, hypertension is increasingly becoming a problem. In 2007, the prevalence of hypertension in Saudi Arabia was 26.1%. Male cases predominated over female instances (28.6 vs 23.9, respectively). Hypertension was more prevalent (by roughly 27.9%) among urban residents than rural residents (occurrence of 22.4 percent). The risk of hypertension increases with age, even if significant and effective preventive actions have been taken [2]. Patients with hypertension need ongoing treatment. Sometimes a lifetime of treatment is necessary. The majority of hypertension medications prescribed are angiotensin II receptor blockers. Here are a few instances of the angiotensin II receptor blockers with high oral bioavailability: Nebivolol is 13%, candesartan is 15%, valsartan is 10%–35%, and olmesartan is 28.6%.<sup>[3]</sup> A highly cardioselective b<sub>1</sub>-receptor blocker with a vasodilatory effect, nitric oxide mediates the action of nebivolol HCL (10 mg). White powder, NN-dimethylformamide (DMF) is soluble in methanol, dimethylsulfoxide, and DMF but not in ethanol, propylene glycol, or polyethylene glycol. The half-life of the active isomer, d-nebivolol, is 12 hours. Nebivolol plasma concentrations peak 1.5–4 hours after administration. Drug binds to protein 98% of the period in vitro. There are no reports of transdermal nebivolol patches. The mechanical properties and medication release pattern of these patches will be examined in vitro.<sup>[4]</sup>

## II. MATERIALS AND METHODS

### a) *Materials*

Nebivolol HCL was purchased from Hyderabad's Hetero Drugs Ltd. We bought Tween 80 from Gattefosse in Mumbai. The reagents used were all of the analytical variety. SD Fine Chemical, based in Mumbai, India, supplied the soyalecithin, Span and Tween 80, Hydroxypropyl E 15 and HPMC E 5, and other products. Other substances and reagents were of analytical quality.

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## b) Methods

### Preparation of Nebivolol HCL Loaded Transfersomes

The flask combination was then given ethanol and chloroform [5]. In the same flask, the drug loading was completed. Each element was dissolved by shaking the solution. The inner surface of the flask was coated with a thin dry lipid layer by a rotary evaporator. The solution was added to an 800 ml rotary vacuum flask evaporator, which was spun at 60 rpm for 30 minutes to create a thin coating on the flask walls.

### Preliminary formulations<sup>[6]</sup>

Sizing, polydispersity index and zeta potential estimation The prepared transfersomes' vesicle size, PDI, and zeta potential were measured by light scattering using the Malvern Master seizer and water as dispersion.

### Entrapment efficiency

After vesicle disruption, the drug concentration in trasferosomes was measured. Trasferosomes containing medication were centrifuged for 30 minutes at 14,000 rpm. The filtrate was analysed. <sup>[7]</sup>.

### Drug content determination

This was measured by dissolving 100 mg of the formulation in 10 mL of ethanol. The blend was tested.

### Preparation of transdermal patch

As a backing membrane, aluminium foil was used to cast the transfersosomal mixtures into transdermal patches. The optimal HPMC: PVA ratio (1:1) was chosen <sup>[8]</sup>. Plasticizer glycerol was added to the mix.

### Characterization of Transfersomal patch

Visual inspection was performed on all of the transdermal patches to ensure that they were of proper colour, clarity, flexibility, and smoothness.

### Uniformity of weight

The average weight of the individual batch was established by weighing five separate patches from the same batch. A considerable deviation from the average weight of five should not be observed in any individual weight<sup>[9]</sup>.

### Moisture content

The film was weighed and then placed in a desiccator with calcium chloride for at least 24 hours to dry out the moisture. The film was weighed several times until it exhibited a consistent weight on the scale. The moisture content was calculated as the difference between the constant weight taken and the beginning weight, and it was expressed as a percentage (by weight) of the total weight of the sample.

### Thickness

The thickness of the patch was measured with the use of Vernier callipers. The thickness of the patch was measured at three distinct locations on the patch, and an average was determined. It is critical to understand the uniformity of patch thickness since it is

directly related to the precision of the dose delivered in each patch.

### Folding endurance

The folding endurance of all of the formulated patches is measured manually by a third party. Using a patch (2 x 2 cm<sup>2</sup>), a strip was cut and folded at the same spot over and over again until it broke. The brittleness of a patch is determined by the number of times it can be folded in the same spot without breaking or cracking <sup>[10]</sup>.

### In vitro dissolution studies

Permeation experiments were carried out in a Franz Diffusion cell of the vertical kind. It was decided to keep a semipermeable membrane on a diffusion cell with an effective diffusion area of 2.303 cm<sup>2</sup> in order to test it. It was maintained at 37 0.5°C throughout the trials with a 22.5 ml phosphate buffer at pH 6.8 as the receptor fluid, which was agitated at 100 rpm in the receptor compartment <sup>[11]</sup>. The amount of drug that permeated was measured by graphing the cumulative amount of drug that permeated against the passage of time<sup>[10]</sup>.

### In vitro skin permeation study

Prior to usage on experiment day, the frozen hog skin samples were thawed and examined for nicks and holes. The skin samples were cut to the proper size and placed on a horizontal type Franz cell on an SFDC-6 transdermal diffusion cell instrument (Logan, USA) with the stratum corneum facing the donor compartment and the dermis facing the receiver cell. Nano-transfersome formulations were applied to the surface of the rats' skin in a non-occlusive way. This experiment used ethanolic phosphate buffer saline (epbs) as the receptor medium (pH 7.4, 20:80). A small magnetic bead moving at a speed of 100 per minute revolutions was used to stir the receiver cell vehicle, which was held at a temperature of 37 degrees Celsius. One millilitre of receiver medium had to be sampled, and an equivalent amount of fresh vehicle had to be added. The samples that were eliminated were assessed using the HPLC technique. A number of metrics were calculated, including the total amount of medication that was absorbed, the lag time (Tlag), the permeability coefficient (Kp), and the enhancement ratio (ER).<sup>[12,11]</sup>.

## III. RESULTS AND DISCUSSION

### a) Screening of edge activators

Span 80, Tween 80, and Labrosol were selected and subjected to additional screening based on the size of the vesicle and the effectiveness with which it was entrapped.

After preparing the nano vesicles using the above-mentioned procedure, they were assessed for their size and entrapment efficiency.

*Table -1:* Formulation of nebivolol hydrochloride transfersomes using various edge activators

<i>Formulation code</i>	<i>S:S-80</i>	<i>S: T-80</i>	<i>S: L</i>	<i>Drug (mg)</i>	<i>Solvent (C:M)</i>	<i>Buffer Solution (ml)</i>	<i>% Entrapment efficiency</i>	<i>Size (nm)</i>
NT1	1:1	-	-	50	1:1	5ml	62± 0.13	257±0.6
NT2	2:1	-	-	50	1:1	5ml	65± 0.04	238±0.9
NT3	3:1	-	-	50	1:1	5ml	69± 0.02	223±0.6
NT4	-	1:1	-	50	1:1	5ml	72± 0.06	186±0.8
NT5	-	2:1	-	50	1:1	5ml	83± 0.16	201±0.6
NT6	-	3:1	-	50	1:1	5ml	89± 0.05	180±0.7
NT7	-	-	1:1	50	1:1	5ml	89± 0.13	157±0.6
NT8	-	-	2:1	50	1:1	5ml	90± 0.16	158±0.8
NT9	-	-	3:1	50	1:1	5ml	93± 0.12	198±0.6

Where n = 3, Mean = SD, S – Soya lecithin, S-80 = Span 80, T-80= Tween 80, L= Labrosol, C- Chloroform, M- Methanol

No. 1 in the table The nanovesicles produced using labrosol (NT7, NT8, and NT9) have shown higher size and improved trapping efficiency as compared to earlier formulations, as shown in table No.1. According to this evidence, increasing the concentration of phospholipids increases the drug's ability to be captured; this is consistent with the facts. The edge activator Labrosol was found to be more suitable for the selected medicine's transfersomal formulation based on the results in Table 1.<sup>[13]</sup>.

#### *Optimization of the formulation by Central Composite Design*

The central composite design having two independent variables (X1&X2) was used to study the effect on dependent variables (Y1&Y2). As per the design (table no.2) total 13 runs were generated out of which 9 with unique combination were observed. The formulations were prepared (table No.3) according to the generated combinations of the design and evaluated for the responses like %entrapment efficiency (Y1) and particle size (Y2) mentioned in table no.- 5.9. The formulations have shown wide range in dependent variables, particle size having range of 140nm-183nm and %entrapment efficiency having 40-96% as shown in table no. 4.



Table-2: Optimization by central composite design

<i>Formulation code</i>	<i>Coded value</i>		<i>Actual value</i>	
	<i>X1</i>	<i>X2</i>	<i>X1</i>	<i>X2</i>
T-N1	-1	1	20	60
T-N2	0	0	40	40
T-N3	0	+1.41421	40	68
T-N4	+1.41421	0	68	40
T-N5	-1	-1	20	20
T-N6	0	0	40	40
T-N7	0	0	40	40
T-N8	-1.41421	0	13	40
T-N9	0	0	40	40
T-N10	0	0	40	40
T-N11	1	-1	40	20
T-N12	1	1	60	60
T-N13	0	-1.41421	40	12
<b>Independent variables</b>	<b>Levels</b>			
	<b>Low (-1)</b>	•	<b>High (1)</b>	
X1- labrosol (%w/v)	20	•	60	
X2-Soya lecithin (%w/v)	20		60	
<b>Dependent variables</b>	<b>Y1- mean size (nm)</b>			
	<b>Y2- percentage entrapment efficiency (%)</b>			

*Table-3:* Formulation of nebivolol hydrochloride transferosomes using central composite design

<i>Formulation code</i>	<i>Labrosol (%w/v)</i>	<i>Soya lecithin (%w/v)</i>	<i>Solvent (C:M)</i>
T-N1	20	60	1:1
T-N2	40	40	1:1
T-N3	40	68	1:1
T-N4	68	40	1:1
T-N5	20	20	1:1
T-N6	40	40	1:1
T-N7	40	40	1:1
T-N8	13	40	1:1
T-N9	40	40	1:1
T-N10	40	40	1:1
T-N11	40	20	1:1
T-N12	60	60	1:1
T-N13	40	12	1:1



Table- 4: Evaluation of nebivolol hydrochloride transferosomes using central composite design

Formulation code	Size (nm)	Zeta potential	PDI	% Entrapment Efficiency
T-N1	166±3.8	-32±8	0.1±5.25	82± 0.13
T-N2	151±6.5	-47±8.2	0.3±5.86	87± 0.04
T-N3	140±2.7	-39±8.2	0.2±3.51	96± 0.14
T-N4	153±2.7	-39±8	0.2±3.51	86± 0.14
T-N5	163±3.2	-51±9	0.1±4.09	92± 0.24
T-N6	151±4.8	-43±9.2	0.2±4.6	87± 0.03
T-N7	151±2.2	-40±8.3	0.3±5.45	87± 0.21
T-N8	180±2.4	-34±8.4	0.4±4.82	92± 0.16
T-N9	151±2.8	-34±7.40	0.2±3.84	87± 0.06
T-N10	151±2.6	-40±6.21	0.1±5.45	87± 0.23
T-N11	148±3.2	-37±7.2	0.1±5.86	86± 0.08
T-N12	157±3.6	-31±8.02	0.2±4.83	88± 0.21
T-N13	183±3.2	-46±9.2	0.2±5.45	80± 0.13

Where n=3

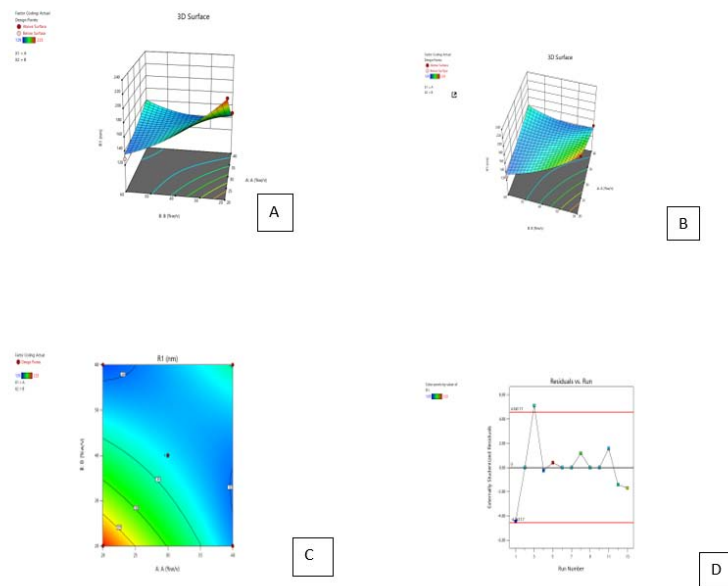


Figure-1: Response surface plots showing the effect of edge activators: lecithin on Particle size (A&B) 3D plot (C) Contour plot (D) Residual plot

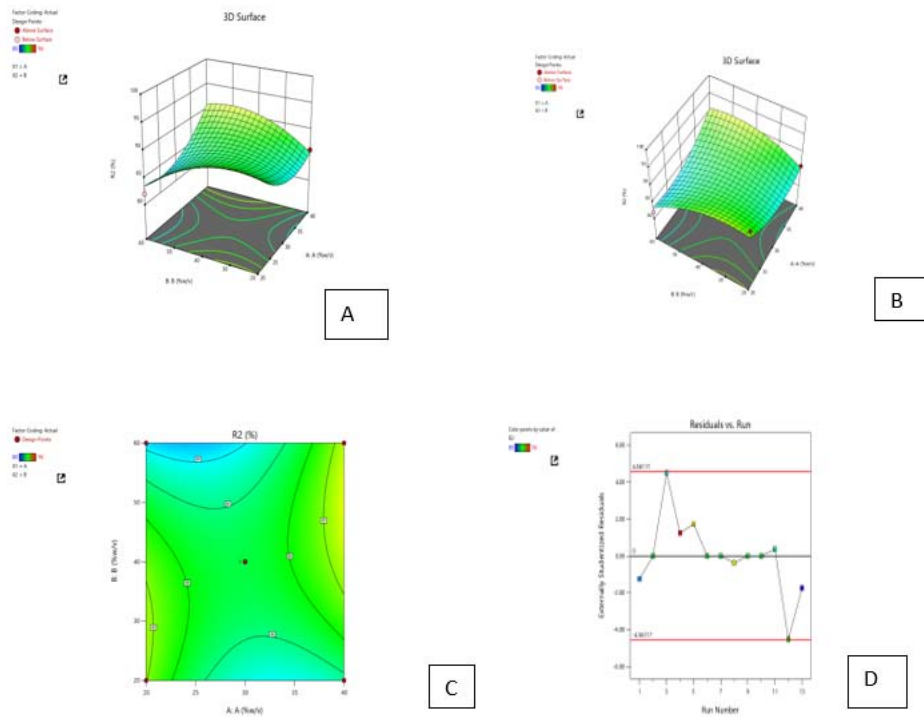


Figure-2: Response surface plots showing the effect of edge activators: lecithin on % Entrapment efficiency (A&B) 3D plot (C) Contour plot (D) Residual plot

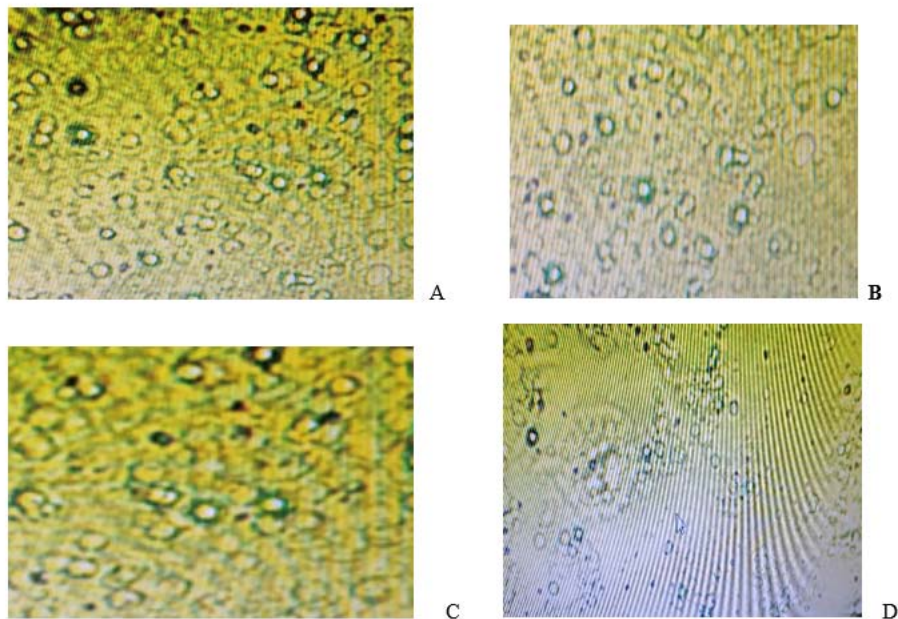


Figure-3: A, B, C & D are the fluorescent microscopic pictures of Nanovesicles

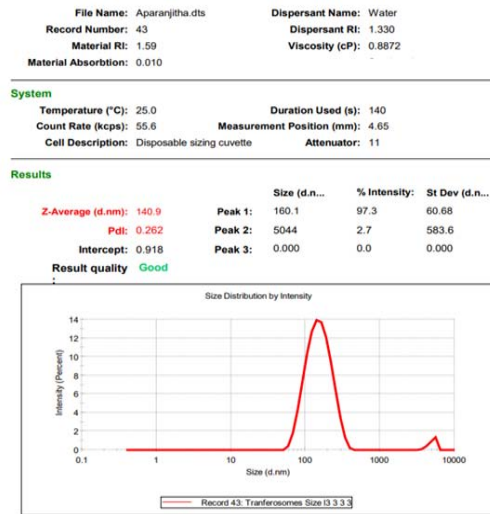


Figure-4: Particle Size determination of Nebivolol hydrochloride nano vesicles with the help of Malvern Zetasizer

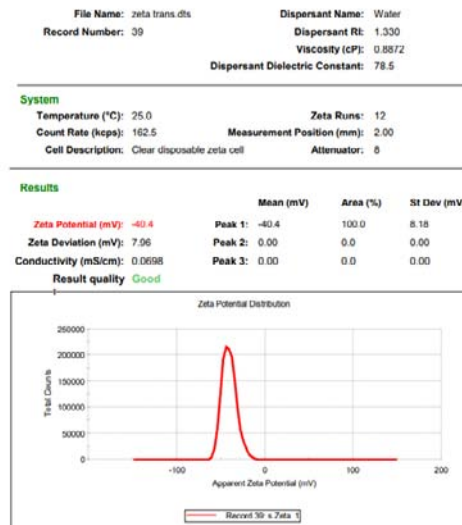


Figure-5: Zeta potential determination of Nebivolol hydrochloride nano vesicles with the help of Malvern Zetasizer.

Preparation of transdermal patches

The transdermal patches were made with varied doses of HPMC E15 and E5. Water and methanol are utilised as the solvent, and polyethelenglycol (PEG)- 400

is used as a plasticizer. Transdermal patches are first made, as indicated in Table-5.

Table-5: Formulation of transdermal patch with Nebivolol hydrochloride

Formulation code	HPMC E5 (%w/v)	HPMC E 15 (%w/v)	PEG-400 (%w/v)	Solvent
PN1	1	-	1.2	Methanol: water
PN2	2	-	1.2	Methanol: water
PN3	2.5	-	1.2	Methanol: water
PN4	3	-	1.2	Methanol: water
PN5	-	1	1.2	Methanol: water
PN6	-	2	1.2	Methanol: water
PN7	-	2.5	1.2	Methanol: water
PN8	-	3	1.2	Methanol: water

As can be seen in table no. 5, the created formulations underwent evaluations for weight variation, thickness, folding endurance, moisture absorption, and percentage drug release. The formulations were made

using the solvent casting method, with the help of the plasticizer PEG-400 (%w/v), the polymers HPMC E 15 and 5, and water as the solvent. [15].

*Table-6:* Evaluation of transdermal patch with nebivolol hydrochloride

<i>Formulation code</i>	<i>Weight(mg) ± SD</i>	<i>Thickness(mm) ± SD</i>	<i>Folding endurance ± SD</i>	<i>Diameter(cm) ± SD</i>	<i>% Drug Release</i>	<i>Moisture absorption (%)</i>
PN1	207± 2.48	0.053 ± 0.002	306 ± 3.52	4.03 ± 0.02	70± 0.14	4.9± 0.52
PN2	184± 2.48	0.050 ± 0.005	302 ± 2.73	4.06 ± 0.06	74± 0.09	5.4± 0.3
PN3	202 ± 2.48	0.048 ± 0.023	304 ± 1.51	4.10 ± 0.08	73± 0.03	5.1± 0.4
PN4	160 ± 2.32	0.047 ± 0.034	300 ± 1.13	4.03 ± 0.02	78± 0.02	4.2± 0.4
PN5	240 ± 2.74	0.054 ± 0.090	308 ± 2.08	4.06 ± 0.06	80± 0.15	3.9± 0.5
PN6	184 ± 2.16	0.048 ± 0.036	308 ± 2.34	4.06 ± 0.03	76± 0.15	3.3± 0.4
PN7	178 ± 1.34	0.050 ± 0.087	306 ± 2.68	4.08 ± 0.09	74± 0.24	5± 0.5
PN8	181 ± 2.21	0.050 ± 0.057	303 ± 1.73	4.05 ± 0.03	70± 0.24	4.6± 0.6

Where n=3

The formulations made with pure medication have drug release in the range of 60-70% invitro across dialysis membrane, according to table No. 6. The folding endurance is unacceptable range for all the prepared formulations [16]. It was discovered that all of the created formulations maintained the proper weight, thickness, and diameter. The transdermal patches' moisture absorption capacity is optimal.

#### *Preparation of transdermal patches*

The formulations with nanocarriers are made using an optimised nano formulation, in which the drug equivalent of 10 mg is added to a mixture of HPMCE15/HPMC E5, plasticizer (PEG-400), solvent (water), and other ingredients as given in table no. 5.18. Evaluation is done on the prepared formulations [17].

*Table-7:* Formulation of transdermal patch with nebivolol hydrochloridenano carriers

<i>Formulation code</i>	<i>HPMCE5 (%w/v)</i>	<i>HPMC E 15 (%w/v)</i>	<i>PEG-400 %w/v</i>	<i>Nano suspension %w/v</i>
TPN1	1	-	1.5	2
TPN2	2	-	1.5	2
TPN3	2.5	-	1.5	2
TPN4	3	-	1.5	2
TPN5	-	1	1.5	2
TPN6	-	2	1.5	2
TPN7	-	2.5	1.5	2
TPN8	-	3	1.5	2

Evaluation of transersomal patches

The evaluation of transersomal patches were carried out for Folding endurance, weight variation,

thickness, moisture content and percentage drug percentage<sup>[18]</sup>.

Table-8: Evaluation of transdermal patch with nebivolol hydrochloride nanocarriers

Formulation code	Weight(mg) ± SD	Thickness(mm) ± SD	Folding endurance ± SD	Diameter(cm) ± SD	% Drug Release	Moisture absorption (%)
TPN1	207± 3.48	0.053 ± 0.001	106 ± 2.52	4.03 ± 0.03	82± 0.05	4.2± 0.2
TPN2	206± 2.48	0.050 ± 0.002	102 ± 1.73	4.06 ± 0.02	86± 0.02	5.4± 0.6
TPN3	204± 2.48	0.048 ± 0.001	104± 2.51	4.10 ± 0.05	89± 0.21	4.8± 0.8
TPN4	195 ± 2.32	0.047 ± 0.001	107 ± 1.73	4.03 ± 0.02	93± 0.24	4.1± 0.4
TPN5	194± 2.74	0.054 ± 0.001	108± 2.08	4.06 ± 0.02	88± 0.15	4.6± 0.3
TPN6	186± 2.16	0.048 ± 0.001	108 ± 2.64	4.06 ± 0.02	86± 0.15	3.9± 0.5
TPN7	193± 1.34	0.050 ± 0.002	106 ± 2.08	4.08 ± 0.02	84± 0.17	3.9± 0.2
TPN8	182± 2.21	0.050 ± 0.001	103± 3.53	4.05 ± 0.04	84± 0.25	4.2± 0.31

Where n=3

The patches made with HPMC E5 have demonstrated better drug release (24hrs) as compared to other formulations, according to the examination of

the transersomal patches[19]. The invitro drug release has improved in the transersomal patches with increases in HPMC E5 concentration.

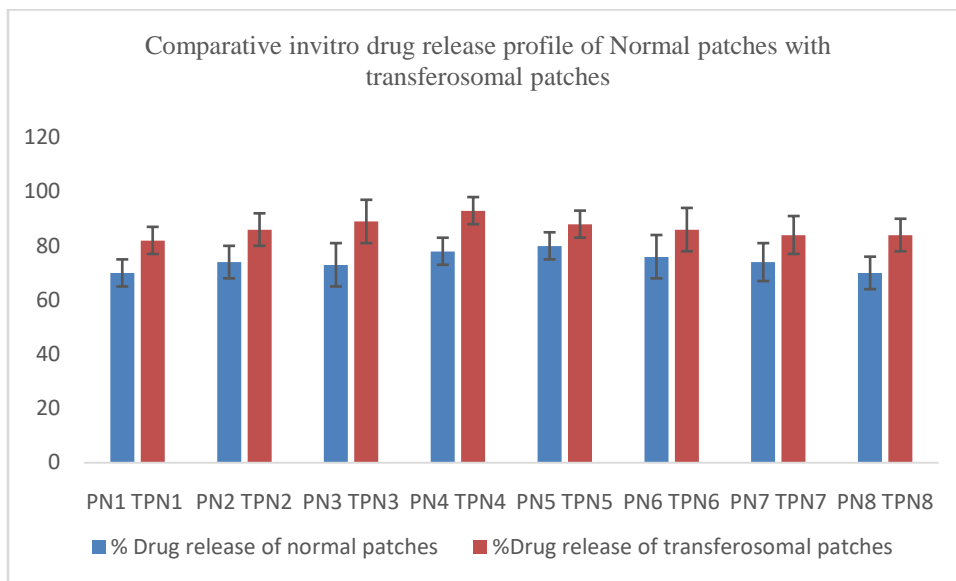


Figure-6: Comparative drug release study of transdermal patches loaded with drug and transersomes.

When comparing the drug release studies using transdermal patches with drugs and transersomal patches, a comparative drug release bar graph like that in Fig. 4.13 is generated. It is clear that the inclusion of flexible nano vesicles that improve diffusion has an impact on the drug release from transersomal patches [21,20].

In-vitro evaluation of transdermal patch with nanocarriers using pig skin

Pig skin was used to assess transersomal patches for skin permeation experiments. Calculations were made for the flux, penetration coefficient, total amount of drug absorbed over the course of 24 hours, enhancement ratio, and lag time (hours)[22].

Table-9: In-vitro evaluation of transdermal patch with nebivolol hydrochloride nanocarriers using pig skin

Formulation code	$Q_{24}(\mu\text{g}/\text{cm}^2)$	Flux( $\mu\text{g}/\text{cm}^2/\text{hr}$ )	Permeation Coefficient ( $\text{cm}/\text{hr}$ ) $K_{px}10^3$	Enhancement Ratio	Lag time(hr)
CONTROL	526±0.43	20±0.65	3±0.5	-	0.6±0.64
TPN1	682.6± 1.44	38± 1.31	9± 0.34	2.4± 0.94	0.2± 0.34
TPN2	656± 1.94	37± 1.46	10.5± 1.04	2.1± 0.62	0.3± 0.23
TPN3	697± 1.32	40± 1.43	10± 1.9	2.7± 0.41	0.2± 0.37
<b>TPN4</b>	<b>733± 1.33</b>	<b>43± 1.2</b>	<b>14.5± 1.2</b>	<b>2.8± 0.32</b>	<b>0.2± 1.39</b>
TPN5	706± 1.35	30± 1.34	13± 1.7	1.6± 0.85	0.3± 0.43
TPN6	657± 1.68	35± 1.52	8.5± 1.9	1.8± 0.72	0.3± 0.53
TPN7	693± 1.84	29± 1.66	9.5± 1.8	1.5± 0.61	0.3± 0.14
TPN8	640± 1.74	35± 1.82	9± 1.3	1.9± 0.81	0.4± 1.45

Where n=3

The results were analysed, and it can be seen from Table No. 9 that all the transdermal formulations have better permeation properties. However, when compared to all the formulations, patches with HPMC E5 of 2.5% with plasticizer 1.5% and nano formulation

have shown better permeation results, having flux of 43 1.2 (g/cm<sup>2</sup>/hr) and permeation coefficient of 14.5 (cm/hr) ( $K_{px}10^3$ )-9, Enhancement Ratio- 2.8, Lag time(hr)-0.2 and  $Q_{24}(\mu\text{g}/\text{cm}^2)$ - 733± 1.33<sup>[23,22]</sup>.

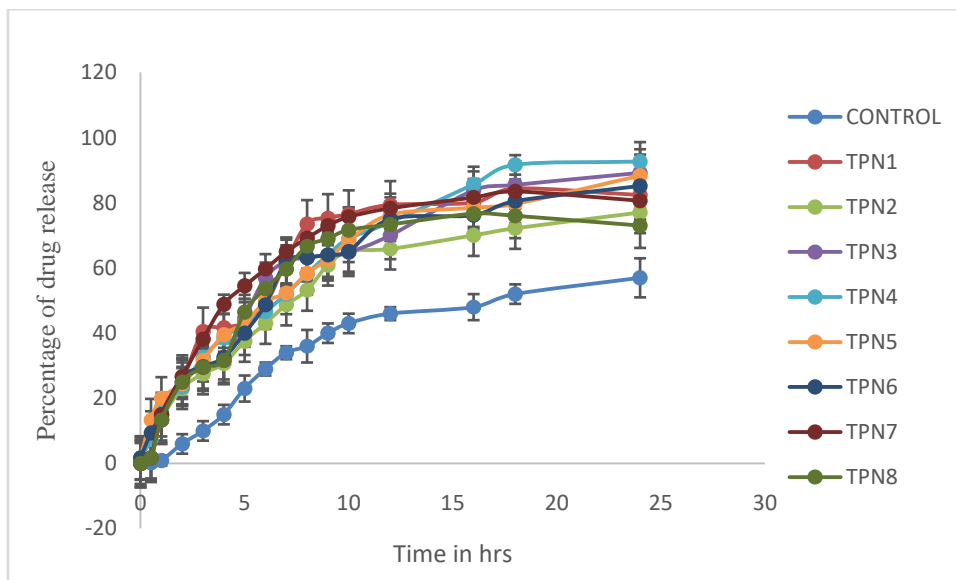


Figure-7: Representation the percentage drug release data of Invitro drug release through skin



Table-10: Model dependent kinetics of nebivolol hydrochloride transdermal patches

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas's equation		Diffusion mechanism
	$R^2$	$R^2$	$R^2$	$R^2$	$n$	
CONTROL	0.81	0.87	0.78	0.83	0.3	Fickian diffusion
TPN1	0.82	0.765	0.89	0.819	0.7	Non-Fickian diffusion
TPN2	0.86	0.78	0.81	0.827	0.6	Non-Fickian diffusion
TPN3	0.82	0.75	0.88	0.894	0.5	Non-Fickian diffusion
<b>TPN4</b>	<b>0.932</b>	<b>0.76</b>	<b>0.91</b>	<b>0.92</b>	<b>0.5</b>	<b>Non-Fickian diffusion</b>
TPN5	0.90	0.828	0.852	0.91	0.6	Non-Fickian diffusion
TPN6	0.86	0.864	0.83	0.84	0.6	Non-Fickian diffusion
TPN7	0.85	0.85	0.85	0.87	0.5	Non-Fickian diffusion
TPN8	0.84	0.86	0.87	0.77	0.5	Non-Fickian diffusion

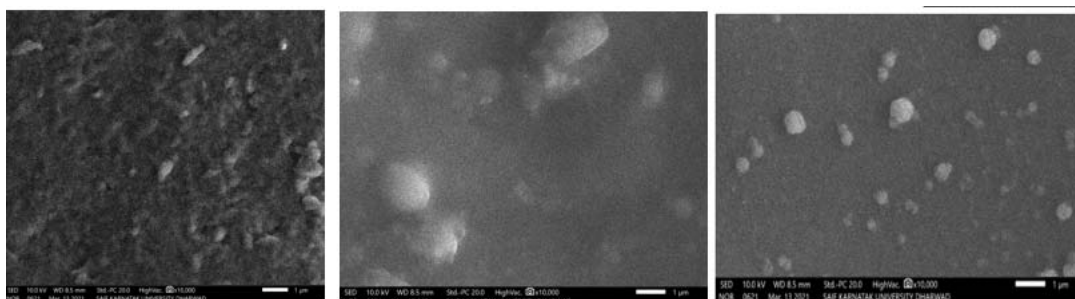


Figure-8: Scanning electron microscopic analysis of Optimized patch

#### Skin irritation study

The animals used in the investigation of cutaneous irritation were guinea pigs. Studies on skin irritation were conducted for 14 days, and the results were tabulated accordingly. The skin irritant caused irritation with both minor and definite erythema, and after 12 days, clearly discernible edoema was created. When compared to this, neither the placebo nor the optimised batch displayed any irritation until 11 days later[24].

#### Stability studies

In accordance with ICH recommendations, the stability studies were carried out using optimised patches under accelerated stability circumstances. Every 0, 15, 30, 60, and 180 days, the patches were examined for moisture absorption, folding endurance,

drug homogeneity, and in vitro drug release through the skin[25].

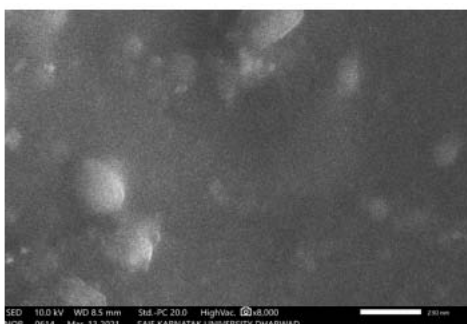
*Table-11:* Stability studies of nebivolol hydrochloride transfersomal patch

Stability conditions	Sampling time	Folding endurance	Drug content uniformity (%)	In vitro drug release (%) through skin	Moisture absorption (%)
Accelerated condition (40 ± 2 C and 75 ± 5% RH)	0	106 ± 2.52	99± 0.02	92± 0.01	4.2± 0.2
	15	102 ± 1.73	97± 0.12	91.6± 0.02	5.3± 0.6
	30	104± 2.51	96± 0.18	91± 0.05	4.4± 0.8
	60	104 ± 1.73	96± 0.14	91± 0.03	5.9± 0.4
	180	104 ± 2.52	96± 0.14	90± 0.02	6.2± 0.3

Where n=3

From the table-11 it is evident that the optimized formulation is found to be stable having good folding

endurance, drug uniformity, In vitro % drug release through skin and moisture absorption.

*Figure- 9:* Representing the SEM imaging of optimized transfersomal patch after stability studies.

#### IV. CONCLUSION

The results of in vitro drug release demonstrate that produced patches released drugs more effectively than conventional transdermal patches. The skin permeation investigations of the improved transfersomal patch (HPMC E5 3% w/v, 1.5% w/v PEG-400, 2% v/v nano suspension, i.e. 40% w/v Labrosol with 68% w/v soy lecithin) revealed flux of 43 (g/cm<sup>2</sup>/hr), permeation coefficient (cm/hr) -14.5, and absorption rate (g/cm<sup>2</sup>/hr), Enhancement Ratio of 2.8, non-fickian diffusion in the Korsmeyer-Peppas model with n = 0.8, and zero order kinetics type of drug release are characteristics of the optimised patches. When compared to the placebo batch and the optimised batch, the optimised formulation has demonstrated better stability. Therefore, based on the results of the current investigation, it can be concluded that transfersomal patches have better drug release qualities than conventional transdermal matrix patches. A regulated drug release of the medication has also been demonstrated via the transdermal patches.

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## Surgery and Diabetes

By Raj Kamal Choudhary

*Introduction-* As incidence of diabetes is increasing, it become a routine to encounter diabetics in every surgical field. Whether it is cataract surgery, laparoscopic cholecystectomy, hysterectomy or cancer surgeries, screening for diabetes is a norm. Diabetes affects pathogenesis of many conditions requiring surgeries like diabetic foot, pyelonephritis and renal abscess, coronary bypass surgeries. Raised blood glucose also affects the course of operation and post-operative course. It affects the healing, infection and other complications. So it is desirable to well maintain the glucose level, so that neither person get ill effect like ketoacidosis or hyperosmolar coma, renal failure, infections nor he get hypoglycemia which adversely affects the life style of the recovering patients. (2, 3)

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# Surgery and Diabetes

Raj Kamal Choudhary

## I. INTRODUCTION

As incidence of diabetes is increasing, it become a routine to encounter diabetics in every surgical field. Whether it is cataract surgery, laparoscopic cholecystectomy, hysterectomy or cancer surgeries, screening for diabetes is a norm. Diabetes affects pathogenesis of many conditions requiring surgeries like diabetic foot, pyelonephritis and renal abscess, coronary bypass surgeries. Raised blood glucose also affects the course of operation and post-operative course. It affects the healing, infection and other complications. So it is desirable to well maintain the glucose level, so that neither person get ill effect like ketoacidosis or hyperosmolar coma, renal failure, infections nor he get hypoglycemia which adversely affects the life style of the recovering patients. (2, 3)

## II. MANAGING BLOOD GLUCOSE DURING PERIOPERATIVE PERIOD

### a) Screening for diabetes in PAC (Pre anesthetic checkup)

It is recommended for all patients above 35 year of age and one below this age with a risk factor (Obesity, hypertension, family history, h/ o GDM, HIV, Physical inactivity).(1) So practically most adult patients

requiring surgical intervention undergo blood glucose estimation. This screening many times make the diagnosis of diabetes for the first time.

If patient is found to have impaired blood glucose, then he can be directed to life style modifications, oral hypoglycemic agents and any further investigation required.

Those who are already diagnose with diabetes, it will be required to do fasting, post prandial blood glucose with HbA1c. (4) These test reflects the control and any untoward effect of glucose will be minimized if it remains in the range. The desired premeal blood glucose is 90-130 mg % and post mealis 140-180 mg%.

### b) Perioperative control of Glucose

Now it is recommended not to stop oral hypoglycemic agents till day before surgery as we used to do previously except for SGLT 2 inhibitors. (5) If blood glucose is fairly controlled then we can continued with these medicines, otherwise it is prudent to switch to insulin. Use of Insulin has few merits and demerits as explained in the box 1. Most hospitals has their own insulin regimen for control of blood glucose in perioperative period depending upon the practices and insulin sensitivity of the individuals.(6)

#### Merits

- I. Short half-life , so can be titrated according to need
- II. More physiologic
- III. Adverse effect can be managed quickly

#### Demerits

- I. Injection phobia to patient
- II. Insulin delivery is a skill

### BOX 1: Merits and Demerits of Insulin use in perioperative period

### c) Effect of anesthesia on diabetes

Now with introduction of newer techniques and novel agents for induction and maintenance of desired level of anaesthesia, it is very easy to control blood glucose. Local, regional, spinal and epidural anaesthesia lessened the systemic complications.

General anaesthesia, long surgeries and labile diabetes increases the chance of glucose imbalance. These can be better tackled by Insulin infusion and hourly blood glucose monitoring.

Insulin use during surgery should be intravenous only because subcutaneous absorption become erratic due to various reasons like hypotension,

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anaesthesia drug effect, and various Intravenous infusion of crystalloids and blood products. During operation / surgery random plasma glucose should be maintained between 140-180 mg %.

d) *Post-operative period and Glucose control*

In post-operative period, we should give insulin because of its merits discussed earlier. In post op period once the patient extubated, start taking oral diet, we can switch to subcutaneous insulin or re-introduce oral hypoglycemic agents gradually. OHA which are

known to cause hypoglycemia like sulphonylureas to be avoided early in the course. It is always better to start multiple subcutaneous insulin injection which is most physiologic and avoid chances of hypoglycemia. (7) Doses can be titrated according to meal, other drugs / fluids influencing blood glucose. Basal insulin is useful to control fasting level. Its steady action decreases the chances of hyperglycemic complications too. Points to be addressed in post-operative period is mentioned in box 2.

1. Eating pattern is not smooth
2. Drugs (fluids, medications and blood products) changes the level of glucose
3. Patient's daily activity is compromised, so it also influence the consumption of glucose.
4. Surgery related effects (pain/immobilization/ anxiety) can affect glucose levels.

*BOX 2:* Points to be addressed in post-operative periods

### III. CONCLUSION

There is no one regimen which can address all patients in all kind of surgeries. So individual patient to be managed with unique approach depending upon the type of surgery, he is undergoing upon. Few basics to be understand in such clinical scenarios as described in box 3.

1. Emergency surgeries not to be postponed for deranged blood glucose.
2. Cancer surgeries are also semi urgent condition, individual risk benefit ratio to be considered before postponing a surgery just because of increased blood glucose.
3. For day care surgeries, no need to stop OHA, and start insulin-we can very well continue OHA, till a day before surgery and reintroduce all one by one as patient oral intake and activity increases.
4. Persons undergoing major surgeries can be switch to insulin (preferably Multi subcutaneous insulin injection (MSII)).
5. Even persons on GLP-1 analogue, DPP 4 inhibitors/SGLT 2 inhibitors or premixed insulin should switch to MSII.
6. During operation, keep patient on Intravenous insulin with hourly glucose monitoring. Target is (140-180 mg %)
7. During post-operative period, gradual recovery demands gradual upgrading of insulin dose and reintroduction of OHA (if needed).

*BOX 3:* Summary of blood glucose control in Perioperative period

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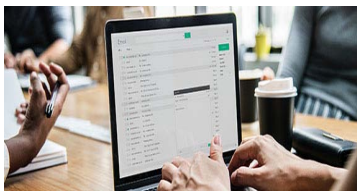
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ASSOCIATE OF MEDICAL RESEARCH COUNCIL is the membership of Global Journals awarded to individuals that the Open Association of Research Society judges to have made a 'substantial contribution to the improvement of computer science, technology, and electronics engineering.

The primary objective is to recognize the leaders in research and scientific fields of the current era with a global perspective and to create a channel between them and other researchers for better exposure and knowledge sharing. Members are most eminent scientists, engineers, and technologists from all across the world. Associate membership can later be promoted to Fellow Membership. Associates are elected for life through a peer review process on the basis of excellence in the respective domain. There is no limit on the number of new nominations made in any year. Each year, the Open Association of Research Society elect up to 12 new Associate Members.



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Global Journals sends a letter of appreciation of author to the Dean or CEO of the University or Company of which author is a part, signed by editor in chief or chief author.



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Associates are authorized to organize symposium/seminar/conference on behalf of Global Journal Incorporation (USA). They can also participate in the same organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent. Additionally, they get free research conferences (and others) alerts.

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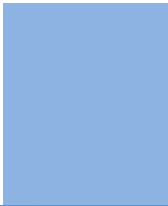
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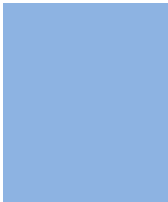
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ASSOCIATE	FELLOW	RESEARCH GROUP	BASIC
<p>\$4800 lifetime designation</p> <hr/> <p>Certificate, LoR and Momento 2 discounted publishing/year Gradation of Research 10 research contacts/day 1 GB Cloud Storage GJ Community Access</p>	<p>\$6800 lifetime designation</p> <hr/> <p>Certificate, LoR and Momento Unlimited discounted publishing/year Gradation of Research Unlimited research contacts/day 5 GB Cloud Storage Online Presense Assistance GJ Community Access</p>	<p>\$12500.00 organizational</p> <hr/> <p>Certificates, LoRs and Momentos Unlimited free publishing/year Gradation of Research Unlimited research contacts/day Unlimited Cloud Storage Online Presense Assistance GJ Community Access</p>	<p>APC per article</p> <hr/> <p>GJ Community Access</p>



# PREFERRED AUTHOR GUIDELINES

## **We accept the manuscript submissions in any standard (generic) format.**

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from <https://globaljournals.org/Template>

Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at [submit@globaljournals.org](mailto:submit@globaljournals.org) or get in touch with [chiefeditor@globaljournals.org](mailto:chiefeditor@globaljournals.org) if they wish to send the abstract before submission.

## BEFORE AND DURING SUBMISSION

Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

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2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author's email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
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7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

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- Findings
- Writings
- Diagrams
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- Illustrations
- Lectures



- Printed material
- Graphic representations
- Computer programs
- Electronic material
- Any other original work

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2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

### Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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### Appealing Decisions

Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

### Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.



### ***Manuscript Style Instruction (Optional)***

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

### ***Structure and Format of Manuscript***

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

- a) A title which should be relevant to the theme of the paper.
- b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
- c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
- d) An introduction, giving fundamental background objectives.
- e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
- f) Results which should be presented concisely by well-designed tables and figures.
- g) Suitable statistical data should also be given.
- h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

- i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
- j) There should be brief acknowledgments.
- k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



## FORMAT STRUCTURE

***It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.***

All manuscripts submitted to Global Journals should include:

### **Title**

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

### **Author details**

The full postal address of any related author(s) must be specified.

### **Abstract**

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

### **Keywords**

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, "What words would a source have to include to be truly valuable in a research paper?" Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

### **Numerical Methods**

Numerical methods used should be transparent and, where appropriate, supported by references.

### **Abbreviations**

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

### **Formulas and equations**

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

### **Tables, Figures, and Figure Legends**

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.



## Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

### PREPARATION OF ELETRONIC FIGURES FOR PUBLICATION

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

### TIPS FOR WRITING A GOOD QUALITY MEDICAL RESEARCH PAPER

**1. Choosing the topic:** In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

**2. Think like evaluators:** If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

**3. Ask your guides:** If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

**4. Use of computer is recommended:** As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

**5. Use the internet for help:** An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



**6. Bookmarks are useful:** When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

**7. Revise what you wrote:** When you write anything, always read it, summarize it, and then finalize it.

**8. Make every effort:** Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

**9. Produce good diagrams of your own:** Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

**10. Use proper verb tense:** Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

**11. Pick a good study spot:** Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

**12. Know what you know:** Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

**13. Use good grammar:** Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

**14. Arrangement of information:** Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

**15. Never start at the last minute:** Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

**16. Multitasking in research is not good:** Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

**17. Never copy others' work:** Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

**18. Go to seminars:** Attend seminars if the topic is relevant to your research area. Utilize all your resources.

**19. Refresh your mind after intervals:** Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.



**20. Think technically:** Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

**21. Adding unnecessary information:** Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

**22. Report concluded results:** Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

**23. Upon conclusion:** Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

## INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

### **Key points to remember:**

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

### **Final points:**

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

*The introduction:* This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

### **The discussion section:**

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

### **General style:**

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

**To make a paper clear:** Adhere to recommended page limits.





### *Mistakes to avoid:*

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

### **Title page:**

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

**Abstract:** This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

*Reason for writing the article—theory, overall issue, purpose.*

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

### **Approach:**

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

### **Introduction:**

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.



*The following approach can create a valuable beginning:*

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

#### **Approach:**

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

#### **Procedures (methods and materials):**

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When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

#### **Materials:**

*Materials may be reported in part of a section or else they may be recognized along with your measures.*

#### **Methods:**

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

#### **Approach:**

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

#### **What to keep away from:**

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



**Results:**

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

**Content:**

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
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- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
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**Approach:**

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If you desire, you may place your figures and tables properly within the text of your results section.

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- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

**Approach:**

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Describe generally acknowledged facts and main beliefs in present tense.

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<i>References</i>	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring



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