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# Formulation and Evaluation of Polymeric Nanoparticles Based Transdermal Hydrogel of Terbutaline Sulphate

**Maha A. Marzouk [1], Asmaa M. El bakry [2], Rania M. El hosary [3], Nehal K. Abd El Rahman[3]***

[1] Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Al- Azhar University, Cairo, Egypt.
[2] Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy and Drug Technology, Heliopolis University, Cairo, Egypt.
[3] Department of Pharmaceutics, National Organization of Drug Control and Research (NODCAR) Former, Egyptian Drug Authority (now), Cairo, Egypt.
** Corresponding Author: nehal1181@hotmail.com

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**Abstract:** Asthma is classified as chronic disease causing inflammation of the airways. Terbutaline sulphate is a synthetic β2-adrenoceptor stimulant used mainly in respiratory medicine. It has short half-life 3.4 hours so the study was done to evaluate the possibility of application of terbutaline sulphate loaded polymeric nanoparticles as transdermal drug delivery systems to give a controlled release dosage form with high rate of skin permeation. The technique that was chosen for the preparation of different formulae was ionic gelation method using tripolyphosphate and chitosan polymers and these formulae were evaluated for their polydispersity index, entrapment efficiency and particle size. The formula with the highest entrapment efficiency and the minimum particle size and PDI was chosen for further measuring of their zeta potential and Transmission Electron Microscope. The nanoparticle suspension was incorporated in hydroxypropyl methylcellulose gel base and evaluated for visual appearance, pH, rheological properties and *in-vitro* release. The hydrogel was then evaluated for *ex-vivo* skin permeation. The chosen formula showed particle size 160.1 nm, entrapment efficiency 70.1, polydespersity index 0.336 and zeta potential 20.1 mv. The hydrogel showed good homogeneity with slightly whitish colour with pH 6.4 and the gel exhibited Higuchi diffusion model. *In vitro* test showed sustained release profile within 24 hours and the Ex-vivo test showed high permeation rate within 3 hours. The Terbutaline sulphate nanoparticle loaded transdermal hydrogel showed high potential for application in transdermal drug delivery with uniform particle size dispersion, controlled release and high permeation behaviour.

**Keywords:** Terbutaline sulphate; ionotropic gelation; Hydroxypropyl methylcellulose; hydrogel; transdermal.



## 1. INTRODUCTION

Transdermal administration has attracted attention as a favourable route for drug delivery due to its convenience, painless self-administration and avoidance of first-pass hepatic metabolism. Drug formulations could be tuned to allow controlled release of drug into the body over an extended period of time thereby decreasing the need of multiple dosing. For these reasons transdermal drug delivery system is considered active area for research[1]. Sometimes, for many drugs such as in case of nitroglycerin patches it lowers the side effect which is obvious in its oral form [2]. Most of the marketed formulations for asthma are inhalation dosage forms and they are short acting thus they uncomfortable choice for nocturnal episodes. However, transdermal systems can provide more safety for drugs with narrow therapeutic window and the systems are generally inexpensive[3]. Transdermal hydrogels loaded with terbutaline sulphate nanoparticles were prepared to give promising effective therapy for treatment of nocturnal asthma particularly [4].

Terbutaline sulphate (TB); β-[(tert-butylamino) methyl]-3,5-dihydroxy-benzyl alcohol ($C_{12}H_{19}NO_3$), a selective $\beta_2$ adrenoceptor agonist The mechanism of the antiasthmatic action of short acting β-adrenergic receptor agonists is undoubtedly linked to the direct relaxation of airway smooth muscle and consequent bronchodilator. Stimulating these receptors leads to activation of adenyl cyclase,



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increase in cellular cyclic AMP, and consequent reduction of muscle tone[5]. It is used for the therapeutic treatment of nocturnal asthma particularly, treat wheezing and shortness of breath.

It is a class II drug according to BCS (Biopharmaceutics Classification System), soluble in water and 0.1N HCl, slightly soluble in methanol and ethanol, insoluble in chloroform, ether and acetone, molecular weight 323.36 g/mol with an oral dose 15 mg/day. It is a drug of choice for the treatment of asthma but it has several drawbacks though it is effective such as short half-life of about 3.6 hours[6]. Also it has low bioavailability 14.8% and its peak plasma level is 1.2µg/ml[7].

It has been reported that a particle size of less than 500 nm is crucial for transdermal delivery[8]. Polymeric nanoparticles (NP) are considered good candidates as drug carriers recently due to their advantages resulting from their nano-size [9]. These advantages include their effective use in controlling drug release, the ability for drug protection against the environment, enhance their bioavailability and therapeutic effect [10]. There are many techniques used to formulate nanosized particles. One of which is the ionotropic gelation technique[11]. It aimed at the formation of chitosan (CS) nanoparticles which depend on electrostatic interaction between amine group of chitosan and of the polyanion tripoly phosphate (TPP) having negatively charged group [12]. This technique had been implemented in many researches as it offers a simple and mild preparation method without the need of addition of any organic or toxic solvents [13] as in case with ampicillin and ondansetron nanoparticles[14,15].

Chitosan nanoparticles are good drug carriers because of their good biocompatibility and biodegradability. Also its tendency to form hydrogels makes it ideal carrier for water soluble drugs [16]. They have the advantage of controlling drug release, which improves drug solubility and stability, enhances efficacy, and reduces toxicity. Because of their small size, they are capable of passing through biological barriers in vivo (such as the blood–brain barrier) and delivering drugs to the lesion site to enhance efficacy. The amino and carboxyl groups in the chitosan molecule can be combined with glycoprotein in mucus to form a hydrogen bond, leading to an adhesive effect. As mucoprotein in mucus is positively charged, chitosan and mucus are attracted to each other to prolong the retention time of drugs and continuous drug release in vivo as well as improve drug bioavailability [17].

Hydrogels are hydrophilic polymers with cross-links which form a network enabling them to absorb large amounts of water [18]. Hydrogels have many advantages as they are biocompatible and gives a controlled drug release profile [19]. Transdermal hydrogels have been utilized due to their effect on enhancing the efficacy, increasing safety, offering high convenience and patient compliance. Many drugs have been incorporated in these formulae due to their advantages for example: Ketorolac which has analgesic and anti-inflammatory behaviour formulated in transdermal hydrogel to avoid the gastrointestinal toxicities associated with oral administration, Ibuprofen transdermal gel provides sustained release of the drug, also celecoxib chitosan hydrogel and Nebivolol hydrochloride loaded nanocarrier hydrogel [20-23].

The aim of work was to formulate a novel transdermal terbutaline sulphate sustained release loaded nanoparticle hydrogel that may overcome the side effects of conventional oral dosage form present at the market and improve the patient compliance.

## 2. MATERIAL and METHODS

### 2.1. Material

TB supplied from EVA pharm, Low molecular weight chitosan and Sodium Tripolyphosphate was supplied from Heinrich's Co., Egypt, Acetic acid and monobasic sodium phosphate from El Nasr Pharmaceutical Co. Hydroxypropyl methyl cellulose from Sigma Aldrich, Egypt. All other materials were of analytical grade.

### 2.2. Methods

*2.2.1. Fourier Transform Infrared Spectroscopy (FTIR):*

FTIR analysis was performed in order to study the compatibility of ingredients used in the preparation of nanoparticles, using a Shimadzu FTIR spectrophotometer (Prestige21, Shimadzu Corporation, Kyoto, Japan). Terbutaline sulphate, chitosan, TPP and their mixture with ratio (1:1:1) was evaluated using FTIR spectrophotometer using potassium bromide disc technique where 1mg of the sample is mixed with 100 mg of dry powdered KBr; the mixture is pressed into a transparent disc and was inserted in the apparatus for IR scan.

*2.2.2. Preparation of TB-NP loaded chitosan suspension*

TB loaded nanoparticles were prepared by the ionotropic gelation method at room temperature with combinations of chitosan and TPP at different ratios 1:1, 3:1, 1:1.5, 1.5:1, 1:3 as shown on table (1) [24]. The particles were formed upon the injection of TPP solution dissolved in water using syringe gauge 27G on chitosan solution in 2% acetic acid containing a defined amount of terbutaline sulphate with continuous stirring on a magnetic stirrer (Jenway 1000, UK) for 60 minutes at room temperature [25]. Then it was centrifuged (Hettich, UK) at 12000 rpm for 15 minutes for 4 times and the formed particles were collected and immediately analyzed for particle

size, polydispersity index (PDI) and Entrapment Efficiency (EE).

**Table (1):** TB-NP formulations with different ratios of CS and TPP

| Formula | CS:TPP |
|---|---|
| F1 | 1:1 |
| F2 | 3:1 |
| F3 | 1:1.5 |
| F4 | 1.5:1 |
| F5 | 1:3 |

*2.2.3. Determination of Particle size, polydispersity index and entrapment efficiency of TB-NP loaded chitosan suspension*

Mean particle size and PDI for the prepared TB loaded formulation was evaluated using dynamic light scattering (Zetasizer, Malvern Instruments, UK).

The entrapment efficiency (EE) of nanoparticles was determined by collecting the nanoparticles formed by ultracentrifugation after being suspended in deionized water (Zenith HC 16B, UK) at 15000 rpm for 30 min. The amount of free TB in the supernatant was measured by UV spectrophotometer (Shimadzu UV 1601, Japan) at $\lambda_{max}$ 277nm. Calculation of TB entrapped in the nanoparticles was done according to equation 1…[26].

$$Entrapment\ (\%) = (TBp - TBf) * 100/_{TBp}$$

The total Terbutaline Sulphate used is TBp and the free Terbutaline Sulphate in the supernatant is $TB_f$.

*2.2.4. Zeta potential and Morphology of TB-NP loaded chitosan suspension*

Both tests were done to the chosen formula F5. Morphological analysis of the selected nanoparticles in suspension was performed using transmission electron microscopy (TEM) (JEM-2100, Japan). The sample was prepared by placing one drop of nanosuspension on a copper grid, the sample was dried at room temperature and stained with phosphate tungsten acid then examined using TEM at 120kv. Digital Micrograph and Soft Imaging Viewer software were used to perform the image capture and analysis[27]. Zeta potential is an important physicochemical property of nanoparticles and can affect their physical stability and mucoadhesive properties. Zeta potential was determined by zetasizer zs (Malvern ZS 90).

*2.2.5. Preparation of NP hydrogel formulations*

The grade of hydroxypropyl methylcellulose (HPMC) used to formulate the hydrogel was (K4M) with concentration (5.5%). The grade and concentration of the polymer was chosen according to previous studies for the preparation of the hydrogel (1, 28). An accurately weighed amount of the polymer was added to distilled water with the application of continuous stirring on a magnetic stirrer. After complete dispersion, it was kept for 24 hours at room temperature for full swelling [29]. TB-NP loaded CS transdermal hydrogel was prepared (each 1gram of the hydrogel containing 3mg of terbutaline sulphate) by the addition of the collected nanoparticles to the previously prepared hydrogels and gently stirred till reaching complete homogeneity [30].

*2.2.6. Characterization of TB-NP loaded hydrogel*

Colour, homogeneity and phase separation were examined with visual observations [31]. The pH of the hydrogel formulations were determined by using digital pH meter (Jenway 3510, Japan). The electrode of digital pH meter was dipped into 0.5 g of the gel formulation and the reading was noted [32].

2.2.7. Determination of drug content

One gram of the formulation was dissolved in 100 ml water, centrifuged at 3000 rpm, filtered then a suitable dilution was measured spectrophotometry against phosphate buffer solution (pH 7.4) as blank at predetermined λmax 277nm [33].

*2.2.8. Determination of gel spreadability*

An accurately weighed amount of each formulation (0.5 g) was localized in a circle with a diameter of 1 cm drawn on a glass plate where a second glass plate was placed over it and then a weight of 500 g was placed to rest on the second glass for 5 min. The diameter (d) after the gel spreads was noted and the result was evaluated with respect to the spreadability area (Si) according to the following equation.

$$Si = d2\pi/_4 \ \ldots\ ^{34}.$$

*2.2.9. Rheological properties*

Rheological experiments were performed to determine viscosity properties of the hydrogel. The viscosity assessments were performed using Brookfield viscometer (DV2T, USA) with a spindle 52 at room temperature [35].

*2.2.10. In-vitro release of TB-NP loaded hydrogel*

The release profile of TB-NP loaded hydrogel was determined using dialysis bag technique [36]. One gram of the gel (containing 3 mg of TB loaded nanoparticles) was placed in a pre-soaked cellulose dialysis membrane bag molecular weight cut off (MWCO) 10kDa tied and immersed in 50mL of phosphate buffer solution PBS (pH 7.4) in a 100ml

beaker. The entity was continuously stirred at 37 °C with a magnetic stirrer 1500 rpm. 1mL of the release medium was removed and replaced with 1mL of fresh PBS solution at time intervals (0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 24, 25 hours). The test was done again with the same technique by using one gram of the hydrogel (containing 3 mg of TB) to compare the effect of the nanoparticles on the release of the drug. The amount of TB was then evaluated by UV spectrophotometer at $\lambda_{max}$ 277nm. The drug release profile was characterized by T50% (time at 50% release) and dissolution efficiency (DE %). T50% was calculated using Curve Expert professional version.

*2.2.11. Kinetic analysis of terbutaline dissolution from TB-NP hydrogel*

The dissolution of the TB-NP from the hydrogel formulation was evaluated by fitting the experimental data to different kinetic equations. The data were analyzed using the linear regression according to:

Zero order kinetics:

$Ct=C_o-k_ot$ … [37]

First order kinetics:

$Ct=C_oe^{-kt}$ … [38]

According to the simplified Higuchi diffusion model:

$C_t=k_h\sqrt{t}$ … [39]

Where, Ct is the total amount of drug dissolved (%) after time t,

$C_o$ is the initial amount of the drug (%),

$K_o$ is the zero order rate constant (% $min^{-1}$),

K is the first order rate constant ($min^{-1}$),

$K_h$ is the rate constant obtained according to Higuchi equation (% $min^{-1/2}$).

The order of the drug dissolution from each gel was determined by calculating the coefficient of determination ($r^2$) in each case. The highest ($r^2$) value represents the order of drug dissolution from the gel.

*2.2.12. Ex-vivo skin permeation studies*

Permeation of the hydrogel containing pure TB and the permeation of the selected TB-NP chitosan transdermal hydrogel through rat skin were investigated. The rat membranes were already prepared and it was immersed in phosphate buffer (pH 7.4). A glass cylindrical tube was fitted into the shafts of dissolution apparatus I (Hanson SR8 plus N/A, USA) (40). The membrane was fixed at one end of the glass cylinders where 1 gm of the TB loaded chitosan nanoparticle hydrogel formulation and the pure drug loaded hydrogel each containing 3 mg of TB was added to test the permeation of each of the hydrogels separately. The receptor cell was filled with 100ml phosphate buffer PH 7.4, the shafts were constantly rotating at 50 rpm and the experiment was executed at 37°C±0.5. Samples (3 mL) from the permeation medium were taken at the given time intervals: 0.25, 0.5, 0.75, 1, 2, 2.25, 2.5 and 3h. The withdrawn samples were replaced with fresh samples of buffer. The sink conditions were maintained through the whole experiment. The permeated drug was analyzed using UV spectrophotometer at $\lambda_{max}$ 277nm. The flux (J) was calculated according to the following equation… [2].

$$flux\ (J) = Amount\ of\ TB\ permeated\ per\ unit\ area\left(\frac{mg}{cm2}\right) \Big/ Time(hr)$$

The enhancement ratio (ER%) was then calculated to evaluate the enhancement in permeation according to the following equation… [3].

$$ER\% = J\ of\ the\ gel\ formula \Big/ J\ of\ TB$$

*2.2.13. Statistical analysis*

All results were carried out in triplicates using ANOVA test and the results were considered significant at p value < 0.05.

## 3. RESULTS and DISCUSSION

### 3.1. Fourier Transform Infrared Spectroscopy (FTIR):

It is important to confirm that TB is not interacting with excipients before formulating new dosage form as this interaction may affect the efficacy of the final product. FTIR spectrum of pure TB, TPP, CS and their physical mixture were recorded as shown in figure (1). The FTIR spectrum of the drug and TPP exhibited the same characteristic bands of pure terbutaline sulphate (OH group at 3330, aromatic ring at 1610 and tertiary butyl group at 1240) which indicates the absence of chemical interaction between them. The FTIR spectrum of the drug and chitosan exhibited the same characteristic bands of pure terbutaline sulphate, however, the characteristic band of OH at 3330 $cm^{-1}$ became broad indicating hydrogen bonding formation between TB and CS.

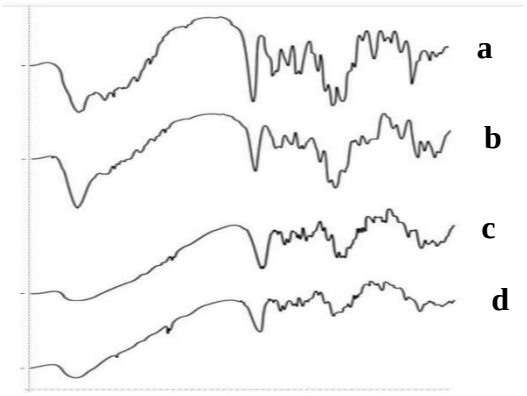

**Figure (1): (a)** TB, **(b)** physical mixture of TB and TPP, **(c)** physical mixture of TB and CS, **(d)** physical mixture of TB, CS and TPP

### 3.2. Particle size, PDI and entrapment efficiency of chitosan nanoparticles suspension

The polydispersity PDI is a measure of the width of the size distribution of particles with values between 0 and 1. It has been elucidated that PDI values near to zero represent homogeneous dispersion and those greater than 0.5 indicate heterogonous particle distribution [41]. Regarding particle size results, the investigated formulations showed particle size ranged from 1622±0.44 to141.8±0.66 nm, PDI with a range of 1±0.20 to 0.336±0.12 and entrapment efficiency ranged from 70.9±0.36 to 28.7±0.34 as shown in table (2). The selection of the appropriate formula was based on the one that have the highest entrapment efficiency, lower PDI and particle size. From the results, it can be concluded that when the mass ratio of CS to TPP was equal (1:1) and when the ratios had close values (1:1.5 and 1.5:1), the PDI values was equal to 1 as it was noticed from F1, F3, F4, they gave low particle size but very high values of PDI indicating heterogeneous dispersion. F2 gave a low PDI value but it was in the microsized range. This may be due to increasing the mass ratio of CS to TPP where the volume of TPP was inadequate which results in instability of the formed particles leading to their aggregation [42]. The best fit formula was F5 with mass ratio (1:3) which gave an evidence that with increasing the mass ratio of TPP the particle size decreased due to increase in the cross linking density between CS and TPP [43]. This ratio gave rise to particle size of 160.1 nm and entrapment efficiency was found to be 70.1.

**Table (2):** Particle size, PDI and Entrapment Efficiency for TB-NP formulations

| Formulae ±SD | Particle size±SD | PDI±SD | EE±SD |
|---|---|---|---|
| F1 | 255±0.51 | 1±0.20 | 65.5±0.09 |
| F2 | 1622±0.44 | 0.45±0.11 | 28.7±0.34 |
| F3 | 141.8±0.66 | 1±0.23 | 45.7±0.21 |
| F4 | 241±0.81 | 1±0.34 | 38.6±0.11 |
| F5 | 160.1±0.47 | 0.336±0.12 | 70.9±0.36 |

### 3.3. Zeta potential and Morphology of TB-NP loaded chitosan suspension

Zeta potential is the overall charge acquired by particles in a particular medium and its value gives the indication of potential physical stability of nanoparticles dispersion. Previous studies have indicated that the higher the values of zeta potential the more stable the nanoparticles produced [44]. Zeta potential gave a result of +20.9mv indicating good stability of the [illegible]ed polymeric nanoparticles.

The [illegible]phology of the nanoparticles optimized formula was investigated through TEM imaging as shown in Figure (2). It could be noticed that the obtained nanoparticles were spherical and uniform in shape. They were well dispersed and their surfaces were relatively smooth. The size was less than 200 nm. Th[illegible]sults were in accordance with the results obtained from the Zetasizer. The obtained particle size could help the nanoparticles to pass through the skin and achieve the desired transdermal effect.

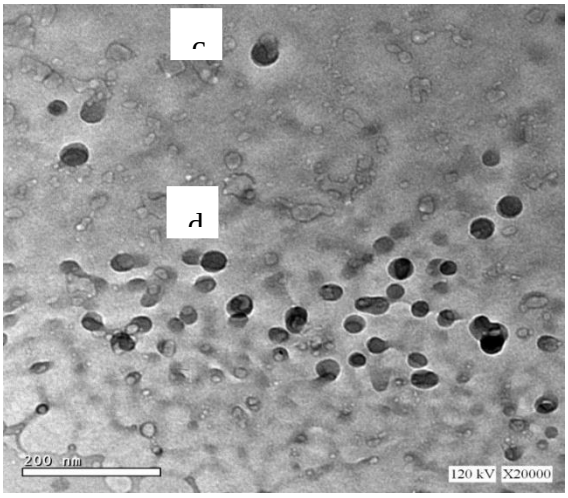


**Figure (2):** TEM micrograph of F5 nanoparticle formulation

### 3.4. Characterization of the prepared hydrogels

The developed hydrogel showed good homogeneity and consistency with absence of any lumps or air bubbles. The colour was slightly whitish which was attributed to the presence of the nanoparticles. The pH of the prepared formulation was found to be 6.4±0.3 which was compatible with skin and avoid irritation making the gel suitable for skin application.

### 3.5. Determination of drug content%

The drug content% of the prepared gel was measured at $\lambda_{max}$ 277 and it was 97.23%±0.65.

### 3.6. Determination of gel spreadability

The value of spreadability indicates that the gel is easily spreaded by small amount of shear which is an essential property in gel formulations. The measured diameter elucidated an indication of the spreadability of the gel and it gave 3.5 cm. So Si value would be 2.74±0.04.

### 3.7. Rheological properties

Rheogram of the prepared hydrogel formulation was plotted; Y-axis is taken to represent the shear rate and X-axis to represent shear stress, as shown in figure (3).

Figure (4) shows the relation between the viscosity and the shear rate of the prepared formulation, it can be noted that there is an inverse relationship between shear rate and viscosity indicating a typical pseudoplastic flow [45]. It must be mentioned that the pseudoplastic flow with thixotropy of hydrogel is favourable for transdermal application as at high shear rate during the rubbing action of the gel on skin, viscosity decrease so it can be easily spread and at the same time the gel is viscous enough to maintain its structure to stay at the site of application.

### 3.8. *In-vitro* release of TB-NP loaded hydrogel

The results of the *in-vitro* dissolution of terbutaline from the prepared hydrogel are shown in figure (5). The nanoparticle hydrogel released about 20% of TB after 2 hours and at $T_{50}$ (time required for release of 50% of drug) after 6 hours. This initial release is characterized by "Burst Effect" which is due to the fact that some of the drug is localized on the surface of the nanoparticles by adsorption which instantaneously dissolved when the particles became in direct contact with the release medium [25]. After this initial burst effect a slower and controlled release which was completed after 24 hours. This biphasic pattern of release is characteristic feature of matrix diffusion kinetics [47]. With respect to TB hydrogel the release was much faster with a significant difference ($p<0.05$) having $T_{50}$ value of 27 minutes. These results showed that the nanoparticles loaded hydrogel had higher value of T50 than the coarse drug loaded hydrogel giving an evidence on the sustained release effect exhibited by the nanoparticles [48]. On the other hand the whole amount of drug was completely released after 3 hours in case of the coarse drug hydrogel.

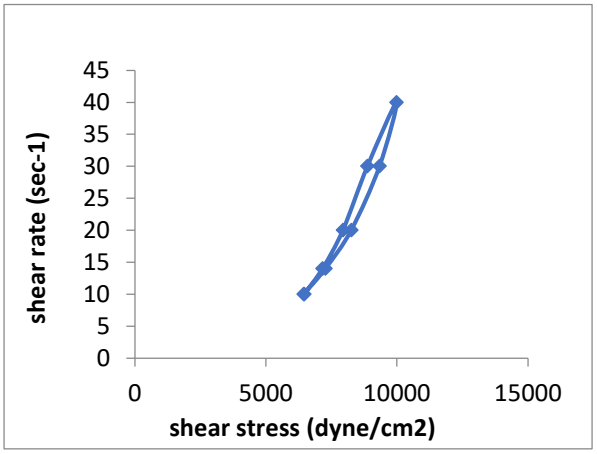


**Figure (3):** Rheogram of HPMC hydrogel

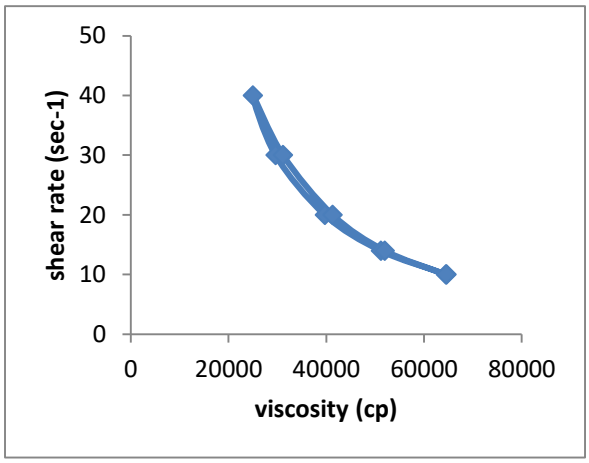


**Figure (4):** Plot of viscosity versus shear rate of HPMC hydrogel

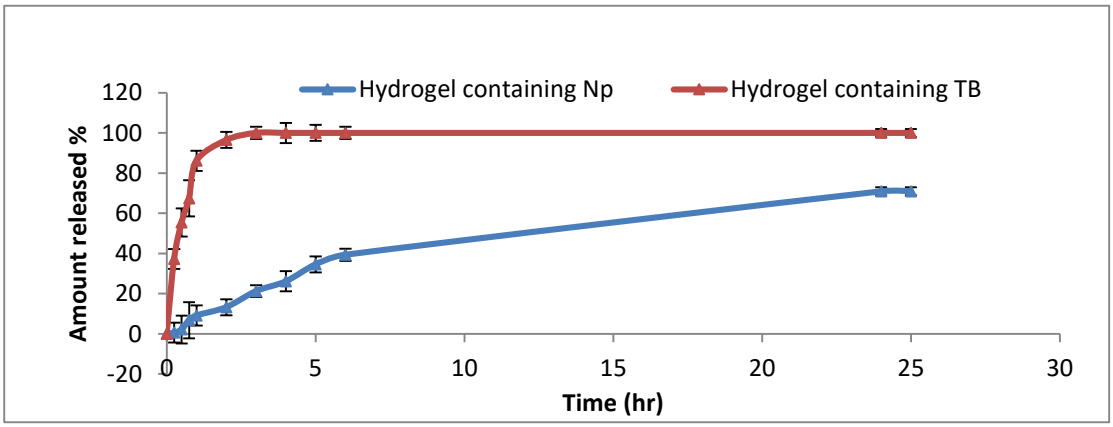


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**Figure (5):** Dissolution profiles of HPMC hydrogel loaded with TB and TB-NP suspension

### 3.9. Kinetic analysis of TB dissolution from TB-NP hydrogel formulations

The *in-vitro* dissolution data for TB-NP hydrogel and TB hydrogel were fitted into different release kinetic and models to determine the type of release of TB from both hydrogels (table 3). It was found that the dissolution from both hydrogel formulations followed Higuchi's model with ($r^2$) value of 0.99 and 0.91 respectively indicating that TB is released by following a diffusion pattern from the hydrogels.

**Table (3):** Release kinetics of TB and TB-NP from the hydrogel

| Release model | $R^2$ of TB hydrogel | $R^2$ of TB-NP hydrogel |
|---|---|---|
| **Zero order** | 0.68 | 0.91 |
| **First order** | 0.77 | 0.48 |
| **Higushi diffusion** | 0.91 | 0.99 |

### 3.10. *Ex-vivo* skin permeation studies

The skin permeation profiles were shown in figure (6). For the prepared formulation, the drug flux from the nanoparticle loaded hydrogel reached its maximum value after 3 hours (850 µg/cm$^2$.hr) while for the pure drug hydrogel at the same time, the drug flux was 622 µg/cm$^2$.hr reaching its maximum value after 4 hours (782 µg/cm$^2$.hr) showing significant difference ($p<0.05$) exhibiting slower rate of permeation. By calculation of the Enhancement Ratio (ER %), it would be concluded that the permeation had improved by 1.366 times. This may be due to the nanocarriers' characteristics as they were able to make a film-like layer covering the skin facilitating the accessibility of drug carriers to the skin and consequently enhancing drug permeation through the stratum corneum [49].

## 5. CONCLUSIONS

In the current work, the TB loaded nanoparticles were successfully prepared using chitosan and TPP by ionic gelation method. The nanoparticles were evaluated for their zeta potential, particle size and entrapment efficiency. They were incorporated into HPMC hydrogel base. The hydrogel showed acceptable pH value, smooth texture and homogeneity and it followed Higuchi diffusion mechanism. From the *in vitro* test, it was found that the hydrogel exhibited sustained release profile. It was concluded from the *ex-vivo* data that the nanoparticle loaded HPMC hydrogel had high permeation rate within 3 hours compared to that of TB which when formulated in HPMC hydrogel it was permeated within 4 hours. On the basis of these findings, the TB-NP loaded hydrogel not only would offer several advantages over conventional drug therapies by increasing patient compliance and escaping the first pass effect but also expected to overcome side effects regarding overdosing and toxicity as it offers a sustained release drug profile in addition it is considered a good candidate to be used in transdermal delivery to enhance permeation through skin.

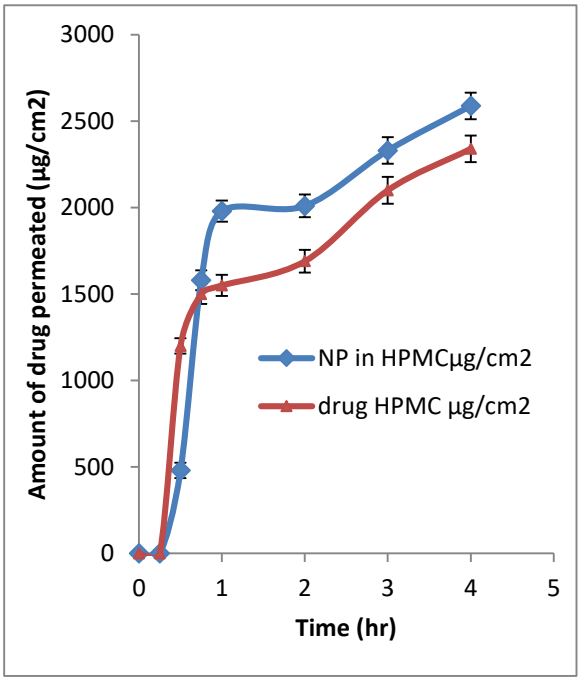


**Figure (6):** Permeation profile of TB loaded HPMC hydrogel and the TB-NP loaded HPMC hydrogel

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**Conflicts of Interest:** The authors have declared that there is no conflict of interest.

**Ethical Statement:** The *ex-vivo* studies were reviewed and approved by the ethical committee of Al-Azhar University's, Faculty of Pharmacy (Registration no. 41).

**Author Contribution:** Dr. Maha Abd Elhamid Marzouk: Supervision and final approval of the manuscript, Dr. Asmaa Mohamed Elbakry: Revision

and adjustment, Dr. Rania Mohamed Elhosary: Revision and adjustment, Dr. Nehal Kamal Eldin Abd El-Rahman: conceived the analysis, collected the data, performed the analysis and wrote the paper.

**List of Abbreviations:** HPMC: Hydroxy propyl methyl cellulose; ER: Enhancement ratio; TB: Terbutaline Sulphate; NP: nanoparticles; TEM: transmission electron microscope; CS: Chitosan; TPP: Tripolyphosphate; FTIR: Fourier Transform Infrared Spectroscopy; PBS: phosphate buffer solution; DE: Dissolution Efficiency; T50: time at 50% release; EE: Entrapment Efficiency; PDI: Polydispersity index.

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