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Evaluation, preparation, and description of chitosan nanoparticles, as well as improving rivaroxaban bioavailability

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ABSTRACT

The aim of the present study is the Evaluation, preparation, and description of chitosan nanoparticles and bioavilibility enhancement of rivaroxaban. Preparation of Rivaroxaban nanoparticles (RB-NPs) were prepared by the ionic gelation method. Different parameters were studied for evaluation, Preparation & description of nanoparticles. The results of the present study showed that the formulation F7 showed the significant results for all the selected parameter as compared to the other formulations. The formulation F1, F5, and F6 showed the highest production yield (52.5, 52.35, and 52.35% respectively) and F7 showed the significant production yield (51.85%), zeta-potential (23.63 mV), entrapment efficiency (99.87), particle size (316.12±2.14 nm) and poly disparity index (0.32). Nanoparticles are solid colloidal drug carriers ranging from 10—1000 nm in diameter and are composed of synthetic, natural or semi-synthetic polymers encapsulating the drug molecule.

1. Introduction

Nanoparticles (NPs) have received therapeutic attention and diagnosis, thanks to their unique physicochemical properties that transform treatment with extremely powerful, toxic, and intelligent effects. Nanoparticles exhibit unique physical, chemical, and biological features in Nano scale compared with their particles at higher concentrations. This condition is caused by large space compared to volume, recycling or stability in chemical process, improved mechanical strength, etc.[1] Chitosan is a polysaccharide containing the flexible units of (1 → 4) Nacetyl glucosamine and glucosamine found in the deacetylation component of chitin. After extensive renovation of its structure, it has been reported to be an effective raw material for the production of nanoparticles with technological advantages. Chitosan NPs are rotten, stable, light, slightly toxic, compact and easy to repair. These are made from natural stainless polymer with chitosan and are approved by GRAS (Best Known for Safe by the United States Food and Drug Administration [US FDA]) of harmful solvent. NPs prepared from chitosan and their derivatives usually have a well-charged area. Chitosan also has some limitations and many of its benefits.[2] Formulation of nanoparticles from chitosan is usually made in low concentrations as the chitosan melts in aqueous solutions at room temperature, no toxic solvents or heat are required. Chitosan nanoparticles have been extensively studied for use in the treatment of cancer. Chitosan nanoparticles can target on tumors specific organs by passive target ion also known as improved the result of permeability and retention (EPR), effective direction, and physical targeting with sensitive

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identification. Inflammation of the polymer is one of the mechanisms that control the release of drugs from chitosan nanoparticle.[3]

Poloxamers, available also under the trademark Pluronics® (BASF), are a class of water-soluble nonionic A-B-A and B-A-B tri block copolymers, where A is poly (ethylene oxide) (PEO) and B is poly (propylene oxide) (PPO). The size and structure of poloxamer assemblies, and their adsorption properties,[4,5] have made them useful in many applications, including, Drug delivery[6], nanoparticle synthesis,[7] cosmetics[8] and emulsion[9] formulation, effective dispersants for inks/pigments[10] and as versatile anti-biofouling coatings,[11] The use of poloxamers in pharmaceutical research is widely researched.

Rivaroxaban (RXB), chemically designated as 5-Chloro-N-{(5S)-2-oxo-3-[4-(3-oxo-4- morpholinyl) phenyl]-1, 3 oxazolidin-5-yl} methyl)-2-thiophene-carboxamide is an orally active direct inhibitor of the activated serine protease Factor Xa, given as mono therapy in the treatment of venous thromboembolism (VTE).[12–14] RXB is lipophilic in nature, exhibiting high permeability across gastrointestinal tract (GIT) and hence classified as a BCS class II drug.[13] Various formulation strategies such as amorphous co-precipitates,[15] co-crystals,[16] lipid solid dispersion,[17] self-micro emulsifying drug delivery systems[18] and, mesoporous dosage form[19] have been explored to improve the limited solubility issues of RXB.

The focus of this investigation is to provide an overview of the chitosan-based nanoparticles for various non-parenteral applications and also to put a spotlight on current research including sustained release. The aim of the present study is the Evaluation, preparation, and description of chitosan nanoparticles and bioavilibility enhancement of rivaroxaban which includes different parameters like formulation studies.

2. Materials and Methods

2.1. Formulation of nanoparticles

Fifteen formulations of Rivaroxaban nanoparticles (RB-NPs) were prepared by the ionic gelation method as described by Calvo et al with slight modifications.[20] Briefly, different concentrations of chitosan and DM were dissolved in 100 ml of 1% (w/v) acetic acid solution, after that TPP was added with different rates to chitosan solution, different quantities of poloxamer 188 were added and stirred at 900 rpm with a magnetic stirrer for 60 min, at the end, the prepared DM-NPs were homogenized by IKA homogenizer (T18 basic, IKA-Werke GmbH, Germany) at different speed for different period of time as assigned by the design. The prepared NPs were washed twice with distilled water then centrifuged using Sigma Laboratory centrifuge, 3K30 (Ostrode am Harz, Germany) at 20000 rpm for 40 min and stored at -80 °C till lyophilized for 24 h using Christ lyophilizer (ALPHA 2–4 lyophilizer, Germany).

2.2. Characterization and evaluation of nanoparticles

1. Production yield: The production yield of the nanoparticles is calculated for each batch by dividing the total weight of product (m) by the total expected weight of drug and polymer. Weight of nanoparticles (m). % yield = Actual yield / Theoretical yield × 100%
2. Determination of Drug content: Sample containing 100 mg equivalent, nanoparticles are dissolved and the volume is made upto100ml buffer. The absorbance of resulting solution is determined using UV spectrophotometer (UV1700 Shimadzu Corporation, japan) and the drug content is estimated.
3. Determination of Particle size: A suitable amount of freeze-dried RB-loaded NPs was dispersed in distilled water (pH 7) by vortex then sonicated using Ultrawave Ltd., water bath sonicator (Cardif, UK). The Accepted Manuscript average of particle size and zeta potential were measured directly by dynamic light scattering (DLS) using a Zetatrac (Microtrac, Inc., PA, USA).
4. Poly disparity index: The size distribution and polydispersity (PDI) index of nanoparticles was determined by dynamic light scattering (DLS), using the zetasizer nano zs90 (malvern instruments, UK) instrument. Samples were analyzed in triplicate, at 25 ° c, with scattered light detected at a 90° angle.
5. Zeta-potential: The zeta potential depends on a variety of factors; in the present case, since the pH of the nanoparticles did not change), the change in zeta potential may be due to the rearrangement among the formulation components, notably the polymer chains. A suitable amount of freeze dried RB-loaded NPs was dispersed in distilled water (pH 7) by vortex then sonicated using Ultra wave Ltd., water bath sonicator (Cardif, UK). The Accepted Manuscript average of zeta potential were measured directly by dynamic light scattering (DLS) using a Zetatrac (Microtrac, Inc., PA, USA). Zeta potential values (in mv) were determined by electrophoresis, by triplicate analysis, at 25°c, using the zeta sizer zs90 instrument.[21]
6. Entrapment Efficiency: Specified weight of RB-loaded NPs was dissolved in (80:20 CAN, water V/V) acetic acid then sonicated for 10 min and filtered, DM was measured by using UV (Agilent technologies, Germany) and the signals were monitored with UV detection at a wavelength of 249 nm" according to the previously reported method (K.-H.H. Cha, et al., 2010). The entrapment efficiency and the loading capacity expressed in percentage were calculated according to Equations

$$\%EE = Actual drug content / Theoretical drug content \times 100$$

% Entrapment efficiency = total amount of drug –

concentration of drug / 100 Total amount of drug ×100

7. SEM: Electron microscopy scanning uses a focus beam of high-power electron to generate various signals at the surface of solid specimens. In most SEM microscopy applications, data is collected from a selected sample surface area and a two-dimensional image is generated showing specific differences in properties texture and orientation of the material and its chemical characterization.

3. Results

3.1. Formulation of nanoparticles

Fifteen formulations of Rivaroxaban nanoparticles (RB-NPs) were prepared by the ionic gelation method as described by Calvo et al with slight modifications as described in section of methods**.**

3.2. Characterization and evaluation of nanoparticles

For characterization and evaluation of all selected formulation different parameter study like production yield poly dispersity index, particle size, entrapment efficiency and zeta-potential were carried out. The results are given in the following table.

The results of the present study showed that the formulation F7 showed the significant results for all the selected parameter as compared to the other formulations. The formulation F1, F5, and F6 showed the highest production yield (52.5, 52.35, 52.35% respectively) and F7 showed the significant production yield (51.85 %), zeta-potential (23.63 mV), entrapment efficiency (99.87), particle size (316.12±2.14 nm) and poly disparity index (0.32). These studies help in the selection of best formulation which can carried out for further pharmacological studies.

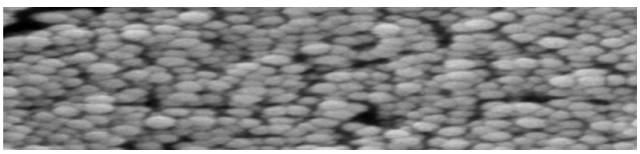

Fig. 1: SEM of formulation F7

4. Discussion

The rapid development of nanotechnology for biological purposes had a tremendous impact on medicine. Nanotechnology enables the manufacture and manipulation of materials on a nanometer scale, thus allowing the development of new tools for the treatment, diagnosis, monitoring, and control of biological systems. This application of nanotechnology in the field of medicine is known as Nano medicine. These NPs have special enhanced physical and chemical properties compared to their corresponding bulk materials. These properties include a high surface area-to-volume ratio and a unique quantum size effect due to specific electronic structures.[22] Nanoparticles (NPs) have received intensive attention in terms of therapeutics and diagnosis, because of their unique physicochemical properties that revolutionize medical treatment with more potent, less toxic, and smart outcomes. The major categories of NPs used for drug delivery and diagnosis, highlighting their fabrication techniques, characterization methods, and physicochemical properties.[23]

The Chitosan NPs are biodegradable, more stable, simple, less toxic, biocompatible and easy to prepare. These are made of a fully biodegradable and biocompatible natural polymer chitosan and also approved by GRAS (Generally Recognized as Safe by the United States Food and Drug Administration [US FDA]).[24]

Nanotechnology is being explored in science for widely different applications. Polymer Nanotechnology has captivated a tremendous interest in many areas such as the pharmaceutical industry and therapeutic innovation among others. Especially, Chitosan Nanoparticles acts as are potential delivery system for hydrophilicand hydrophobic drugs due to its outstanding physicochemical and biological properties. It can control and sustain release the drug during the transportation and at the site of localization, altering distribution of the drug and subsequent clearance to achieve increasein drug therapeutic efficacy and reduction in side effects. Chitosan based formulations have been used for the delivery of pharmaceutically active ingredients, nucleic acids,[25] protein therapeutics and antigens.[26] After studying these reports, the present investgation was designed.

The present investigation is carried out for Evaluation, preparation, and description of chitosan nanoparticles and bioavailability to enhance the bioavailability of the poorly soluble drug Rivaroxaban by using different excipient which includes pre-formulation, formulation, optimization and characterization.

Chitosan is a natural material has great attention in pharmaceutical and biomedical fields because of its advantageous biological properties, such as biodegradability, biocompatibility and nontoxicity.[27,28] It is a cationic polysaccharide obtained by partial deacetylation of chitin, the major component of crustacean shells. Chitosan is composed of N-acetyl-2-amino-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose linked by (1 → 4)-b-glycosidic bonds.[29] The use of chitosan as biomaterial is sustained primary by its biocompatibility and non-toxicityalready proven. Based on the acute toxicity test results, Rao and Sharma[30], stated that chitosan is a safety material. Furthermore, it has been already approved by the Food and Drug Administration for applications as wound dressing.[31]

Table 1: Formulation of nanoparticles

S.No.	Formulation	Drug (mg/ml)	Chitosan (%)	Tripolyphospahte (%)	Poloxamer
1	F-1	1	1	0.35	50
2	F-2	0.5	1	0.35	50
3	F-3	1	1	0.35	10
4	F-4	0.5	1	0.35	10
5	F-5	1	1	0.35	50
6	F-6	1	1	0.35	50
7	F-7	0.5	1	0.35	50
8	F-8	1	1	0.35	10
9	F-9	1	1	0.35	10
10	F-10	0.5	1	0.35	10
11	F-11	0.5	1	0.35	50
12	F-12	0.5	1	0.35	10
13	F-13	0.75	1	0.35	30
14	F-14	0.75	1	0.35	30
15	F-15	0.75	1	0.35	30
16	F-16	0.75	1	0.35	30
17	F-17	0.75	1	0.35	30

Table 2: Characterization and evaluation of nanoparticles

S.No.	Formulation	Production yield%	Zeta-Potential (mV)	Entrapment Efficiency%	Particle size(nm)	Poly disparity index
1	F-1	52.5	14.03	42.34	286.13±2.24	0.20
2	F-2	51.85	19.22	73.86	296.12±2.16	0.18
3	F-3	12.35	15.24	58.12	306.11±2.34	0.15
4	F-4	11.85	10.67	71.07	296.13±2.54	0.09
5	F-5	52.35	18.01	68.76	297.14±3.14	0.12
6	F-6	52.35	17.98	45.68	312.12±2.54	0.23
7	F-7	51.85	23.63	99.87	316.12±2.14	0.32
8	F-8	12.35	13.66	77.39	314.13±2.14	0.14
9	F-9	12.35	12.58	63.24	311.14±2.14	0.16
10	F-10	11.85	18.21	97.18	313.17±2.14	0.19
11	F-11	51.85	16.34	78.23	310.19±2.14	0.21
12	F-12	11.85	12.98	72.96	316.21±2.14	0.30
13	F-13	32.1	20.13	86.7	316.23±2.14	0.29
14	F-14	32.1	19.54	84.21	316.25±2.14	0.22
15	F-15	32.1	21.54	86.37	316.26±2.14	0.28
16	F-16	32.1	20.00	86.37	316.27±2.14	0.17
17	F-17	32.1	10.67	86.37	316.28±2.14	0.27

In formulation studies fifteen formulations of Rivaroxaban nanoparticles (Rivaroxaban -NPs) were prepared by the ionic gelation method as described by Calvo et al with slight modifications[20] Considerable information was provided by the statistical design to optimize the formulation after obtaining and analyzing the results. For Characterization and evaluation of all selected formulation different parameter study like production yield poly dispersity index, particle size, entrapment efficiency and zeta-potential were carried out. The amount of chitosan, and TPP were optimized to prepare Rivaroxaban-NP formulation based on the responses like particle size, PDI, and zeta potential. Results showed the responses for the factors and the results acknowledge that particle size and zeta potential were increased with an increase in the concentration of TPP and chitosan. A linear increase in the polydispersity index is seen with higher concentrations of acetic acid and this was in accordance with the literature.[32,33]

The factors temperature and stirring speed greatly affect zeta potential. The increase in stirring speed and temperature decreased the viscosity of the dispersion that leads to a decrease in zeta potential due to structural instability.[34] The zeta-potential varied from 10.67 mV. to 21.54 Mv whereas particle size varied from 286.13±2.24 nm to 316.28±2.14 nm. Entrapment of drugs on polymeric drug carriers is primarily influenced by the nature of drug-carrier interactions. However, the release of drugs

from formulations under in vitro as well as in vivo conditions largely depends on the drug binding as well as the composition of the formulations, including the excipients. The entrapment efficiency varied from 42.34% to 99.87%. The formulation F1, F5, and F6 showed the highest production yield (52.5, 52.35, 52.35% respectively) and F7 showed the significant production yield (51.85 %), zeta-potential (23.63 mV), entrapment efficiency (99.87), particle size (316.12±2.14) and poly disparity index (0.32).

SEM has been used to determine the particle size distribution, surface texture and to examine the morphology of the fractured or sectioned surface. The same generally used for generating three-dimensional surface relief images derived from secondary electrons. The examination of surface of polymeric drug delivery can provide important information about the porosity and micro texture of given formulation.

5. Conclusion

Nanotechnology has produced an extremely important impact on Nano biomedicine and the diagnosis/treatment of disease. Nanoparticles are solid colloidal drug carriers ranging from 10—1000 nm in diameter and are composed of synthetic, natural or semi-synthetic polymers encapsulating the drug molecule. Due to its biodegradability, biocompatibility, easier formulation techniques and versatility in application aided with low toxicity chitosan offers certain advantages over others amongst the polymeric carriers for Nano particulate drug delivery.

6. Source of Funding

None.

7. Conflicts of Interest

The authors state that they have no conflicts of interest.

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