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Fabrication of Vesicular System of Ciprofloxacin for Possible Delivery to the Colon: an *In Vitro* Evaluation

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Abstract: It is recognized that antibiotics like ciprofloxacin can slow the progression of inflammatory bowel disorders (IBD). However, when used at clinical doses, ciprofloxacin can have unfavorable side effects, such as tendonitis and tendon rupture. Without targeted delivery, IBD drugs may be absorbed into the systemic circulation, resulting in severe side effects. Ciprofloxacin will work better and have fewer side effects if administered directly to the colon, the site of the ailment. This study seeks to engineer a ciprofloxacin hydrochloride-loaded vesicular delivery system termed proniosomes for possible colon targeting. Ciprofloxacin hydrochloride loaded proniosomes were prepared with Span® 60, Tween® 60, and cholesterol by the slurry method via two carriers (dextrin and Neusilin® FH2). They were targeted to the colon via the Eudragit® FS 30D-coated capsules. *In vitro* evaluations [particle size, polydispersity index (PDI), entrapment efficiency, granule properties, scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), and drug release study] were carried out. The results showed particle sizes of < 100 nm and a PDI of <0.3 for optimum formulations. FTIR investigations detected hydrogen bonding between the drug and other formulation excipients. All the formulations demonstrated excellent entrapment efficiency (>80%). Eudragit® FS 30D-coated capsules (containing proniosomes) showed negligible/minimal release in the simulated gastric fluid pH 1.2 and phosphate buffer pH 6.8 media, but profound release in the colonic media-Phosphate buffer (pH 7.4). Ciprofloxacin hydrochloride was successfully targeted to the colon via the vesicular system.

Keywords: Ciprofloxacin; proniosomes; vesicular drug delivery system; dextrin; Neusilin® FH2; Eudragit® FS 30D.

1. Introduction

Vesicular drug delivery platforms have advanced significantly in the area of innovative drug delivery. This is because drug encapsulation in vesicular structures prolongs the medication's time in the systemic circulation while reducing toxicity through selective uptake [1–5]. One way to describe vesicular drug delivery systems is as highly organized assemblies of one or more concentric lipid bilayers created when particular amphiphilic building blocks are exposed to water. The innovative vesicular system aims to focus the active ingredient at the site of action while also delivering the drug at a pace required by the body to produce a therapeutic effect during treatment [6,7]. Additionally, vesicular drug delivery systems operate as sustained release systems by delaying the elimination of quickly digested medications. This lowers the cost of therapy by increasing drug bioavailability, particularly in the case of poorly soluble pharmaceuticals. They can also entrap both hydrophilic and lipophilic medications. Vesicular drug delivery platforms provide a variety of benefits, but they are also severely constrained by the following: low drug loading efficiency and drug leakage during storage [8-10].

As an alternative to niosomes, proniosomes have drawn much interest from researchers. The drawbacks of liposomes or niosomal dispersion, such as physical instability demonstrated by vesicle aggregation, fusion, size fluctuations, and drug leakage, can be overcome using the proniosomal technique [5,11,12]. Proniosomes are water-soluble carrier particles covered with a surfactant in a dry, free-flowing composition. A non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol are combined, and then the mixture is hydrated in aqueous media or bodily fluids, resulting in microscopic lamellar formations. Proniosomes are available as a dry powder, which adds to their ease in delivery, storage, processing, and packing. They also offer the greatest flexibility and are stable [7, 13].

Numerous studies have focused on colon-targeted drug delivery in recent years because of its potential to enhance the management of local disorders affecting the colon while reducing systemic side effects [14-16]. Irritable bowel syndrome (IBS), Crohn’s disease (CD), and ulcerative colitis are a few examples of colon-related illnesses. Because these medications are delivered directly to the colon rather than first being digested in the upper gastrointestinal (GI) tract, a higher concentration can reach the colon with less systemic absorption. Colonic mucosa is known to aid in the absorption of various medications, and the colonic contents have a longer retention duration (up to 5 days), making this organ a suitable site for drug delivery [17].

Ciprofloxacin hydrochloride (CIP-HCl) (Figure 1) is a well-known second-generation fluoroquinolone antibiotic with a broad range of activity. It is highly bactericidal, has a broad spectrum, and can permeate most tissues and accumulate in cells. It is a promising and effective medication with strong antibacterial activity [17,18]. IBD may develop due to microbial dysbiosis in the gut microbial population brought on by intestinal immune system malfunction. Antibiotics may affect the course of IBD by reducing bacterial densities in the gut lumen and changing the composition of the intestinal microbiota to favor beneficial bacteria, since intestinal bacteria play a significant role in the development of IBD. Additionally, they aim for particular microorganisms thought to be involved in the etiology of IBD. Ciprofloxacin is one of the antibiotics that have been found useful in the management of IBD [19-21].

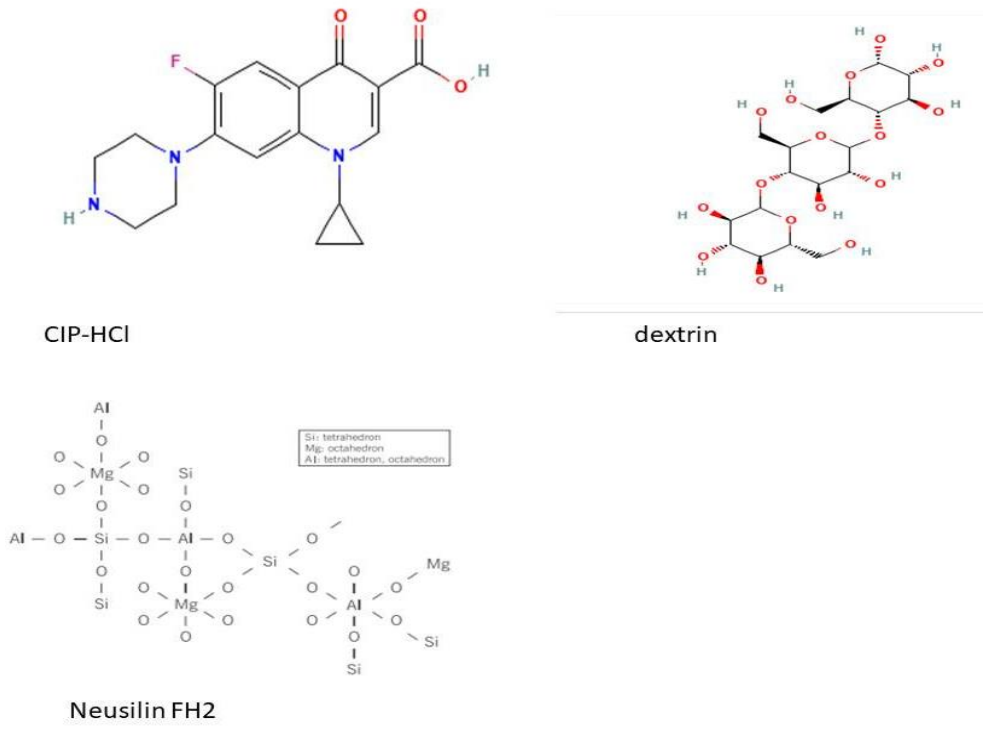


Figure 1. Chemical structure of ciprofloxacin hydrochloride, dextrin, and Neusilin®.

Nanoparticles such as the proniosomes can prolong the circulation period and reduce side effects by improving drug encapsulation and targeted delivery [20]. Some researchers have reported the delivery of ciprofloxacin as a niosomal suspension in decreasing antibiotic resistance in ciprofloxacin-resistant methicillin-resistant *Staphylococcus aureus* [18]; however, there is a shortage of information on the colon-targeted delivery of ciprofloxacin vesicular carrier for the improved management of IBD. Furthermore, ciprofloxacin hydrochloride, when given conventionally, is associated with side effects such as tendonitis, tendon rupture, photosensitivity, inhibition of cartilage growth in fetuses and children, oral thrush, and QT prolongation however targeting it to the colon may minimize these side effects from occurring as negligible quantity of the drug is released before it gets to the colon and thus a reduced amount of the drug is given and less side effects are experienced [20,21]. This study seeks to fabricate ciprofloxacin-loaded proniosomes for possible colon-targeted delivery. To contribute to knowledge in this field, the objectives of this study are (i) to formulate ciprofloxacin-loaded proniosomes, (ii) engineer them for possible colon targeting via the utilization of Eudragit FS-30D capsules, and (iii) to conduct *in vitro* evaluations on the formulations.

2. Materials and Methods

2.1. Materials.

The following materials were used in this study: ciprofloxacin HCl, Span® 60 and Tween® 60 (Aladdin, China), Eudragit® FS 30D coated capsules (Evonik, Germany), cholesterol (Abcams, United Kingdom), dextrin (BDH, England), Neusilin® FH2 (BASF, Germany), analytical grade ethanol, sodium chloride, concentrated hydrochloric acid (Sigma Aldrich, Germany).

2.2. Methods.

2.2.1. Preparation of ciprofloxacin hydrochloride-loaded proniosomes.

Proniosomes were created utilizing the slurry process [11]. In a nutshell, accurately weighed portions of a lipid mixture with different ratios of cholesterol and Span/Tween 60, as presented in Tables 1 and 2, were added to a beaker containing 3 ml of ethanol. The mixture was heated to 40°C and stirred on a magnetic stirrer to help dissolve the lipid combination, followed by adding CIP-HCl (800 mg). After dissolution of the drug, dextrin (for dextrin-based formulations) or Neusilin® FH2 (for Neusilin-based formulations) was added to make a thick dispersion, which was further agitated until the organic solvent had entirely evaporated (Figure 2). The resulting powder was then further dried overnight in a desiccator.

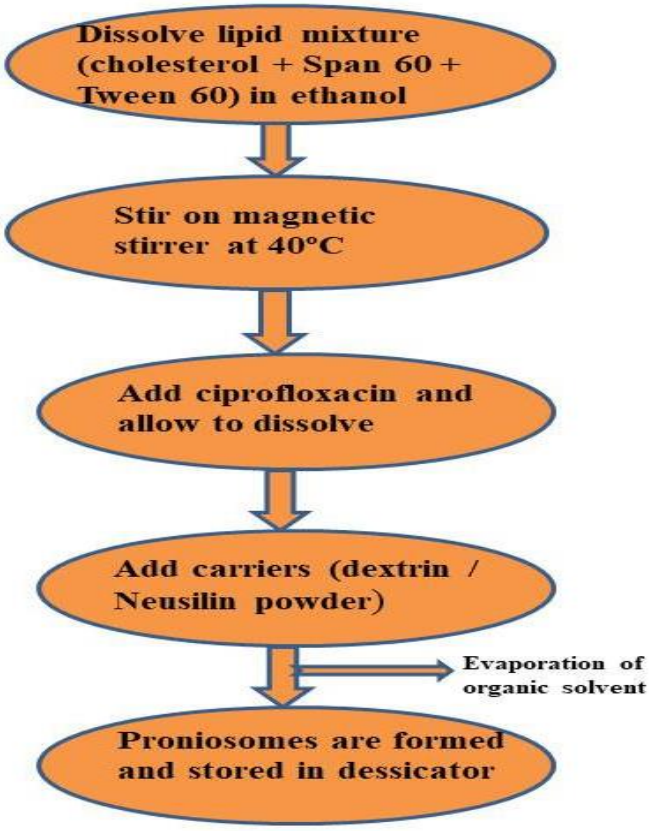


Figure 2. Flow chart for the preparation of proniosomal formulations.

Table 1. Formula for dextrin-based formulation.

Formulation number	Surfactant: cholesterol	Tween 60 (g)	Span 60 (g)	Cholesterol (g)	CIP-HCl (g)	Carrier (dextrin) (g)
DF1	1:1	-	1	1	0.8	5
DF4	1:1	1	-	1	0.8	5
DF7	1:1	0.5	0.5	1	0.8	5
PLACEBO	1:1	0.4	0.4	0.8	-	4

Table 2. Neusilin-based formulation.

Formulation number	Surfactant: cholesterol	Tween 60 (g)	Span 60 (g)	Cholesterol (g)	CIP-HCl (g)	Carrier (Neusilin FH2) (g)
NF3	1:1.5	-	0.8	1.2	0.8	5
NF4	1:1	1	-	1	0.8	5
NF7	1:1	0.5	0.5	1	0.8	5
PLACEBO	1:1	0.4	0.4	0.8	-	4

2.2.2. *In vitro* evaluation of CIP-HCl-loaded proniosomes.

2.2.2.1. Granulation properties of CIP-HCl-loaded proniosomes.

The powdered proniosomes were weighed in 5 g portions. Each one was added to a measuring cylinder with a capacity of 50 mL. The cylinder was dropped on a wooden platform three times at intervals of two seconds from a height of one inch, and the volume occupied by the powders was measured, indicating the bulk volume. Then, tapped volume was determined by tapping on the wooden platform until the volume of the powder remained constant. The tapped density and bulk density are calculated in equations 1 and 2. Other granulation parameters, such as flow rate, angle of repose, Hausner's quotient, and Carr's compressibility index, were also determined.

$$Bulk\ density = \frac{mass\ of\ powder}{voiume} \quad (1)$$

$$Tapped\ density = \frac{mass\ of\ powder}{volume} \quad (2)$$

2.2.2.2. Entrapment efficiency/drug loading capacity.

The entrapment efficiency was determined by hydrating 100mg of powdered proniosomes in 5 mL phosphate buffer (pH 7.4). A 1ml volume was centrifuged at 17709 g for 5 min. The supernatant was then analyzed for the free drug at a wavelength of 249 nm [22] using a UV-Vis spectrophotometer (Jenway, Bibby Scientific Limited, UK). All the assays were done in triplicate. The entrapment efficiency and drug loading capacity were calculated according to equations 3 and 4 below.

$$Entrapment\ efficiency = \frac{total\ drug\ loaded - drug\ in\ supernatant}{total\ drug\ loaded} x100 \quad (3)$$

$$Drug\ loading\ capacity = \frac{amount\ of\ drug\ entrapped}{Total\ weight\ of\ the\ nanoparticles} x\ 100\ \% \quad (4)$$

2.2.2.3. Particle size/polydispersity index (PDI).

The mean size and size distribution of freshly prepared niosomes from proniosomes were determined by photon correlation spectroscopy using a zeta nanosizer (Malvern Instruments, Malvern, UK). Each sample was diluted with water to the proper concentration, and size analysis was conducted at a detection angle of 90°C and a temperature of 25°C. The device was used to determine the "niosomes' particle size and polydispersity index.

2.2.2.4. Scanning electron microscopy (SEM).

The scanning electron microscope (SEM) (Hitachi Japan, Model 3400N) was used to analyze and identify the surface morphology of the carriers (dextrin and Neusilin® FH2) and the ciprofloxacin-loaded proniosomes. Thin layers of gold particles were applied to the samples, which were then placed on a glass slide, and SEM pictures were captured at a magnification of 500x [23].

2.2.2.5. Fourier transform infrared spectroscopy (FTIR).

FTIR was used to investigate drug-excipient interactions or compatibility investigations. The FTIR spectra of the drug (CIP-HCl), blank proniosomes, and CIP-HCl-loaded niosomes were obtained using an infrared spectrophotometer. The formulations were made in KBr disks (2 mg sample/200 mg KBr) using a hydrostatic press at 275790.292 Pascals of force for 4 min, and the spectrum was generated between the wavelength range of 4000 and 400 cm^{-1}.

2.2.2.6. Encapsulation of proniosomes.

Pre-coated Eudragit® FD30S capsules (Evonik, Germany) were also employed for the colon delivery of the proniosomes. A 300 mg quantity of the proniosomes equivalent to 50mg of CIP-HCl was filled into these capsules and stored till further use.

2.2.2.7. *In vitro* drug release of ciprofloxacin proniosomal formulation.

The *in vitro* drug release study used the rotating basket method with the coated capsules trapped in the basket. The dissolution studies were done sequentially at intervals in simulated gastric fluid (SGF) (pH 1.2) and phosphate buffer (pH 6.8 and 7.4) for a period of 10h. The temperature and speed were maintained at 37 ± 1°C and 100rpm, respectively. At predetermined time intervals, 5ml was withdrawn and replaced with a corresponding fresh medium to maintain constant volume. Each of the samples obtained for each drug was then assayed using the UV-spectrophotometer (Jenway, Bibby Scientific Limited, UK) at the predetermined wavelength of 249nm. All the assays were done in triplicate.

2.2.2.8. Statistical analysis.

Data were analyzed using SPSS Version 26.0 (SPSS Inc., Chicago, IL, US). Values were presented as mean ± SD (standard deviation). Means were compared via the one-way ANOVA, and $p < 0.05$ was considered statistically significant.

3. Results and Discussion

3.1. Granulation properties.

The granulation properties generally indicate fair passable flow behavior. Refer to Table 3. The angle of repose measures the internal friction or cohesion of the particles. It is high if cohesive and other forces are high, and vice versa. Generally, if the angle exceeds 50°, the powder will not flow satisfactorily, while materials with values near the minimum, circa 25°, flow easily and well [11,24,25]. It should be noted that two different carriers (dextrin and Neusilin® FH2) were used. The dextrin-based proniosomes showed the best flow under gravity, followed by Neusilin-based proniosomes. All the batches showed acceptable granulation qualities as determined by the results of the angle of repose, 'Hausner's quotient (HQ), and 'Carr's compressibility index (CI). HQ values below 1.25 imply good flow, and those above 1.25 denote bad flow. For HQ levels between 1.25 and 1.5, a glidant must be added to increase flow. The flow scale of powder and granulations has been rated outstanding for CI values between 5 and 15%, acceptable for 12 to 16%, and fair to passable for 18 to 21%, while between 23 and 35% is rated as poor, 33 to 38% is rated as very poor, and values

>40% are rated as extremely poor [26]. HQ and CI are helpful indices for evaluating the flow characteristics of medication granules and powders. The general flow behavior of the proniosomes was sufficient to guarantee free and easy flow into the capsules.

Table 3. Granule properties of CIP-HCl-loaded proniosomes.

Batches	Bulk Density(g/ml)	Tapped Density(g/ml)	Flow Rate(g/min)	Angle of repose	Hausner's quotient	Carr's compressibility index
DF1	0.50	0.56	4.20	21.8	1.12	12
DF4	0.42	0.50	2.33	23.6	1.19	16
DF7	0.36	0.42	4.39	23.6	1.17	14.3
DPlacebo	0.36	0.63	1.12	36.9	1.75	42.8
NF3	0.63	0.71	3.76	28.1	1.13	11.3
NF4	0.56	0.63	3.97	25.6	1.13	11.1
NF7	0.56	0.63	4.95	28.1	1.13	11.1
NPlacebo	0.57	0.62	3.57	21.8	1.09	8.1

*DF 1- DF 7 – Dextrin-based proniosomal formulations containing ciprofloxacin NF 3 – NF 7 – Neusilin-based proniosomal formulations containing ciprofloxacin.

3.2. Entrapment efficiency and drug loading capacity.

The CIP-HCl-loaded "proniosomes' encapsulation efficiency (EE) ranged from 79.40 ± 0.82 to 92.90 ± 0.73%, and their drug loading capacities were between 12.70 ± 0.05 and 14.90 ± 0.12% (Table 4). Most of the proniosomal formulations had EE > 80%. Drug entrapment is influenced by the preparation method, chain length, and hydrophilic head group size of the non-ionic surfactant. In general, proniosomes with long alkyl chain surfactants are reported to have increased entrapment efficiency [27]. The Neusilin®-based proniosomes (NF4) showed significantly higher entrapment ($p < 0.05$) of 92.9% compared to all other batches. Tween® 60, which has a high HLB value of 14.7 and a long alkyl chain in batch NF4, may cause greater entrapment. The ease of hydration with the carriers may have also contributed to the high EE seen. Proniosomes are more likely to entrap more medications than traditional niosomes since the carriers are known to impart a larger surface area and flexibility [28]. Dextrin and Neusilin® have imparted the advantage of a larger surface area. A significant difference ($p < 0.05$) in EE was generally observed across the batches when the data were subjected to Post Hoc tests. The ratio of the amount of medicine that is trapped to the total weight of polymers used in the formulation is known as the drug loading capacity (DLC) [29]. There was no significant difference in DLC between any of the batches.

Table 4. Entrapment efficiency and drug loading capacity of CIP-HCl-loaded proniosome**s.**

Batches	EE (%)	DLC (%)
DF1	86.10 ± 0.82	13.80 ± 0.13
DF4	86.80 ± 0.41	13.90 ± 0.06
DF7	88.80 ± 0.65	14.20 ± 0.10
NF3	87.90 ± 0.24	14.10 ± 0.04
NF4	92.90 ± 0.73	14.90 ± 0.12
NF7	79.40 ± 0.33	12.70 ± 0.05

*DF 1- DF 7 – Dextrin-based proniosomal formulations containing ciprofloxacin, NF 3 – NF 7 – Neusilin-based proniosomal formulations containing ciprofloxacin.

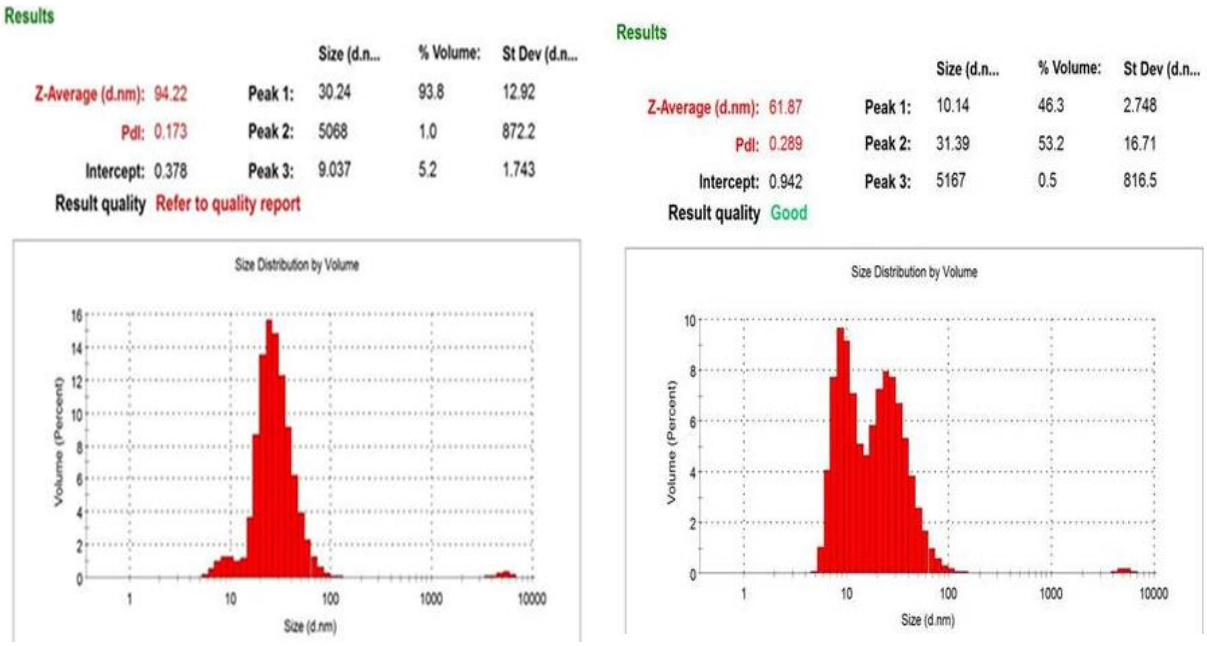
3.3. Particle size and polydispersity index(PDI).

Particle-size analysis of the proniosomal formulation was 94.22 nm and 61.87 nm for dextrin and Neusilin®-based formulations, respectively. On the other hand, the polydispersity index was 0.173 and 0.289 for dextrin and Neusilin®-based formulations, respectively (Table 5, Figure 3). The particle size of the dextrin-based proniosomal formulation was significantly

smaller ($P < 0.05$) than that of the Neusilin®-based formulation. Both dextrin and Neusilin®–based proniosomal formulations had particle sizes (< 100 nm) in nano size ranges. Nano-sized particles are easily taken up at the cellular level. They possess unique features such as prolonged blood circulation and reduced enzyme degradation *in vivo* [30]. Our findings imply that the proniosomal nanoparticles may accumulate at the site of inflammation in inflammatory bowel disease (IBD) [20,21]. The polydispersity index values (PDI) are used to indicate the consistency and quality of dispersed systems. When PDI is closer to zero, it implies the formulation is monodispersed and homogenous [31,32]. The polydispersity indices of both formulations were less than 0.3, which is considered ideal and indicates a narrow size distribution. This shows the formulation is monodispersed [33,34]. Therefore, the formulations may have a great tendency for stability *in vivo* (See Figure 3).

Table 5. Particle size and polydispersity index of CIP-HCl-loaded proniosomes.

Batches	Particle size (nm)	PDI
DF7	61.87 ± 0.82	0.170 ± 0.002
NF3	94.22 ± 0.18	0.290 ± 0.006



NF 3 **DF 7**

Figure 3. Particle size distribution of Neusilin and Dextrin–based proniosomal formulations loaded with ciprofloxacin.

3.4. Scanning electron microscopy (SEM).

The morphology of the proniosomes was investigated using SEM. Figures 4 and 5 display the SEM findings. The carriers are usually coated with a thin surfactant coating during the production of proniosomes [35]. According to our findings, the dextrin or Neusilin powder was coated with a surfactant and lipid mixture. Some researchers have also documented aggregation of individual nanoparticles that appeared smooth-surfaced and close to spherical to polyhedral shape for maltodextrin-based formulations loaded with resveratrol [36]. Generally, the proniosomal formulations seen in the SEM results showed thicker surfaces, depicting that the carrier or powders were coated with the surfactant and cholesterol mixture. In summary, the dextrin-loaded proniosomes appeared as aggregates of porous

particles, while Neusilin-based proniosomes appeared cracked and flaky. This finding agreed with the report of Shruthi and his team [36]. The porous structure of the dextrin-loaded proniosomes may suggest ease of hydration *in vivo*.

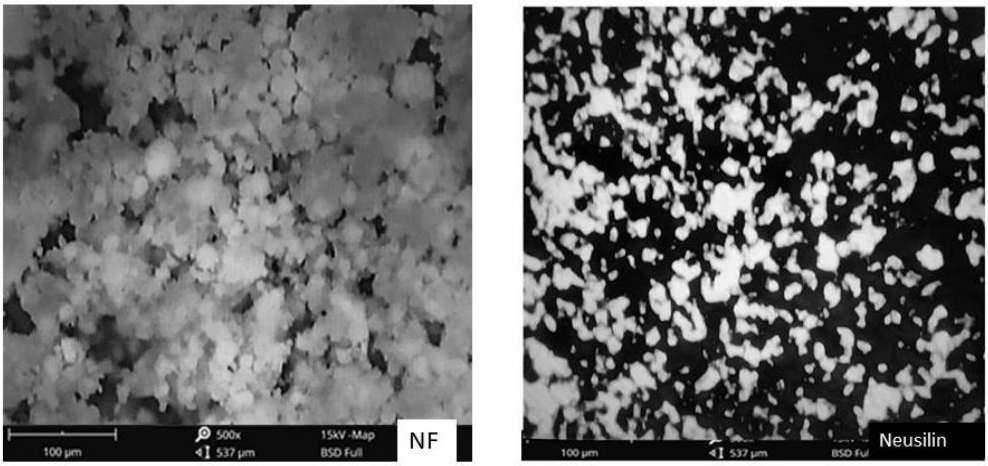


Figure 4. Morphology of Neusilin-based ciprofloxacin proniosomal formulation (NF) and morphology of Neusilin carrier via SEM.

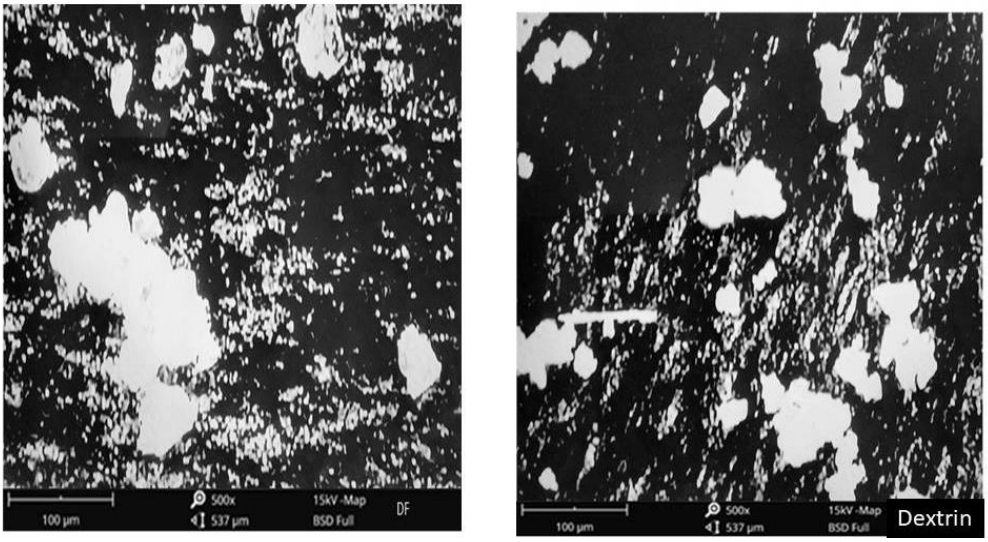


Figure 5. Morphology of Dextrin-based ciprofloxacin proniosomal formulation (DF) and morphology of dextrin carrier via SEM.

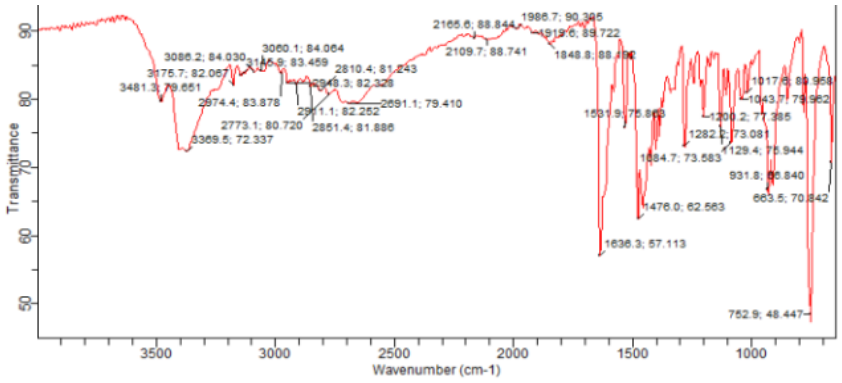
3.5. Fourier transform infrared spectroscopy (FTIR).

Drug–excipient compatibility studies were done via FTIR. CIP-HCl spectrum showed peaks at 3369.5–3481.3 cm^{-1}, 2691.1 and 2901.1 cm^{-1}, 1636.3 cm^{-1}, 1476 cm^{-1}, 1200–1282 cm^{-1}, 1017.6-1043 cm^{-1}, depicting O-H stretch, C–H stretch, N-H bend, C-O Bend, O–H bend, and C–F stretch respectively. Our findings were similar to other research reports [37,38]. The FTIR spectra of Neusilin and dextrin-based formulations were similar to the spectrum of ciprofloxacin; however, an additional peak was seen at 1738.9 and 1736.9 cm^{-1}, respectively, suggesting C=O Stretch (Table 6, Figures 6 and 7). The blank proniosomal preparation without CIP-HCl showed broader O–H peaks than drug-loaded formulations. This pattern was more obvious with the dextrin–based formulation without the drug. This could be linked to the reported presence of the OH group on the dextrin (refer to Figure 1) [39]. Nevertheless, Neusilin powder doesn't possess an OH functional group [40]. Generally, hydrogen bonding interactions occur between the proniosomal components and the drug. This

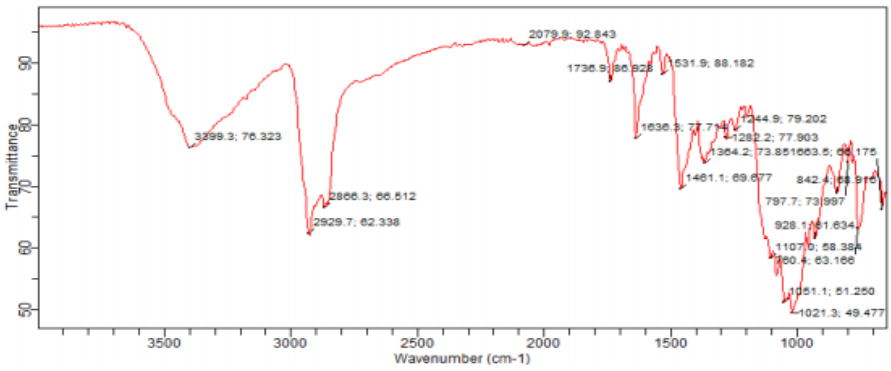
pattern was consistent with other research reports [30,41]. According to the FTIR studies, no undesirable interactions were detected between the drug and excipients.

Table 6. FTIR of ciprofloxacin HCl and proniosomal formulations.

CIP-HCl		Dextrin-based proniosomal formulations		Neusilin®-based proniosomal formulations	
Absorption band (cm $^{-1}$)	**Functional group**	**Absorption band (cm $^{-1}$)**	**Functional group**	**Absorption band (cm $^{-1}$)**	**Functional group**
3369.5 and 3481.3	O–H Stretch	3399.3	O–H Stretch	3339.3	O–H Stretch
2691.1 and 2901.1	C-H Stretch	2806.3 and 2929.7	C-H Stretch	2929.7	C-H Stretch
1636.3	N-H Bend	1736.9	C=O Stretch	1738.9	C=O Stretch
1476	-O Bend	1636.3	N-H Bend	1636.3	N-H Bend
1200 - 1282	O–H bend	1461.1	C-O Bend	1423.8	C-O Bend
1017.6 - 1043	C–F Stretch	1244.9 and 1282.2	O–H bend	1084.7	C–F Stretch
		1020 -1107	C–F Stretch		



(a)



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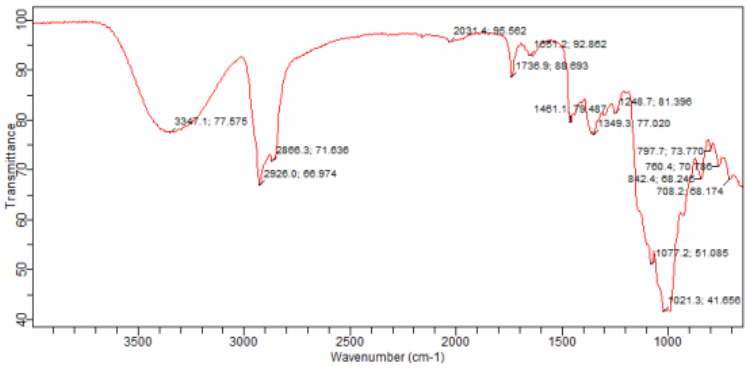
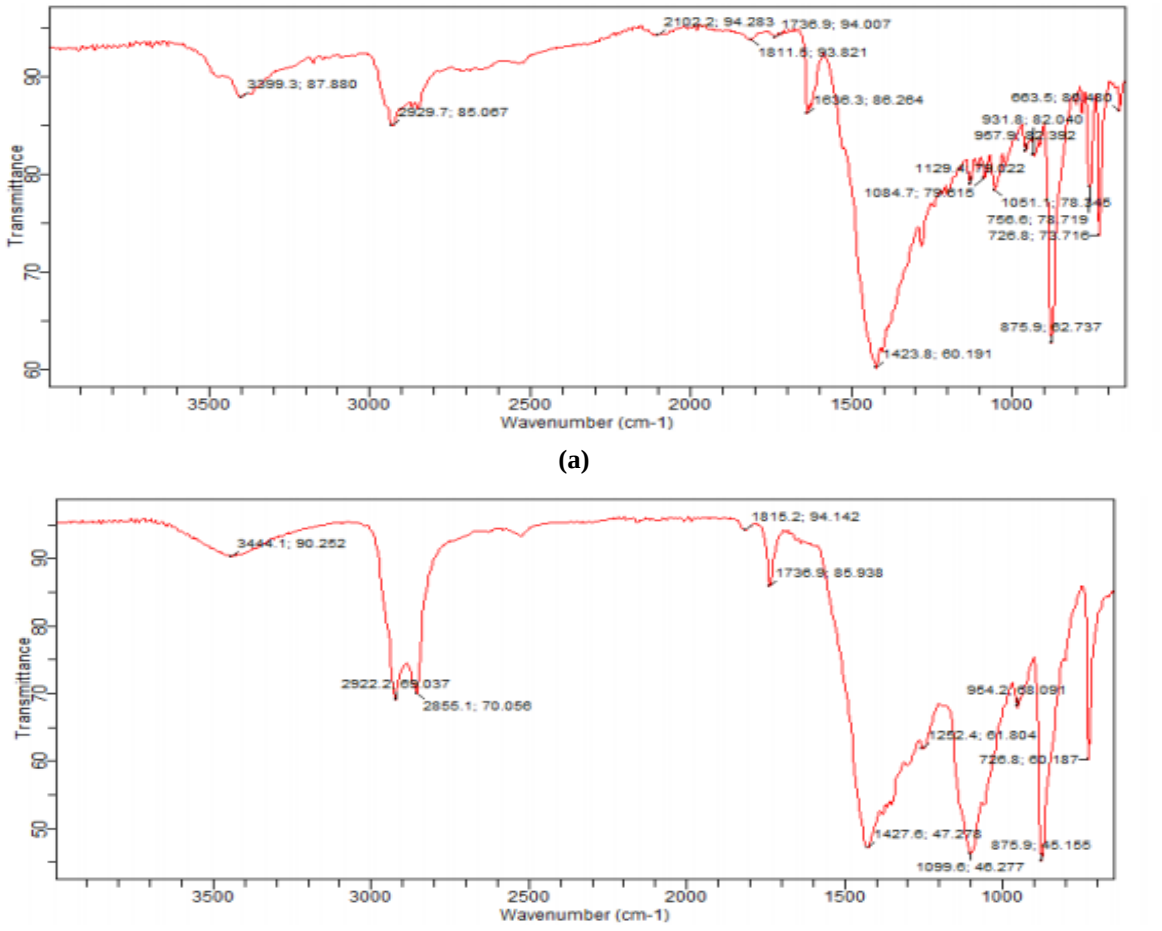


(c)

Figure 6. FTIR of **(a)** Ciprofloxacin hydrochloride; **(b)** dextrin-based proniosomal formulation loaded with ciprofloxacin hydrochloride; **(c)** dextrin-based proniosomal formulation loaded without ciprofloxacin hydrochloride.



(a)

(b)

Figure 7. FTIR of **(a)** Neusilin-based proniosomal formulation loaded with ciprofloxacin hydrochloride; **(b)** Neusilin-based proniosomal formulation loaded without ciprofloxacin hydrochloride.

3.6. In vitro drug release of ciprofloxacin proniosomal formulation.

The pH-dependent drug release from the encapsulated ciprofloxacin proniosomes was evaluated at pH values of 1.2 (for 2h), 6.8 (for 3h), and 7.4, simulating the stomach, small intestine, and colon, respectively. In the first 2 h in pH 1.2, drug release for both formulations was less than 1%, the next 3 hrs in pH 6.8, drug release was less than 5% and 4% for Neusilin and dextrin-based formulations, respectively (Figure 8). Higher drug release was seen in pH 7.4 from the 6th h to the 10th h. At the end of the 10th hour, drug release was 30.92% and 37.01% for Neusilin and dextrin-based proniosomal formulations, respectively. An *in vitro* dissolution study was conducted to understand the *in vitro* drug release profile of the proniosomal formulations encapsulated in Eudragit FS 30D-coated capsules. Eudragit® FS 30D is a poly(meth) acrylate-based copolymer with gastro-resistant properties. They are insoluble at low pH but become more soluble at high pH [42]. This formulation was intended to avoid the release of the drug in the gastric and upper intestinal region but to release the drug slowly in the lower part of the intestine, maximizing drug concentration in the colon in the treatment of IBD. The results showed the resistance feature of Eudragit® FS 30D coated capsules in pH 1.2 and 6.8 media, as negligible releases were seen. However, higher release was obtained in the colonic (pH 7.4) medium because Eudragit® FS 30D is a pH-dependent polymer that dissolves in an environment above pH 7.0 [43]. Summarily, the dextrin-based formulation showed a higher drug release than the Neusilin counterpart due to the solubility

of dextrin in an aqueous medium [44]. The lower drug release seen in Neusilin-based formulations may be due to the poor water solubility of Neusilin and, consequently, low desorption from its matrix, giving rise to lower drug release.

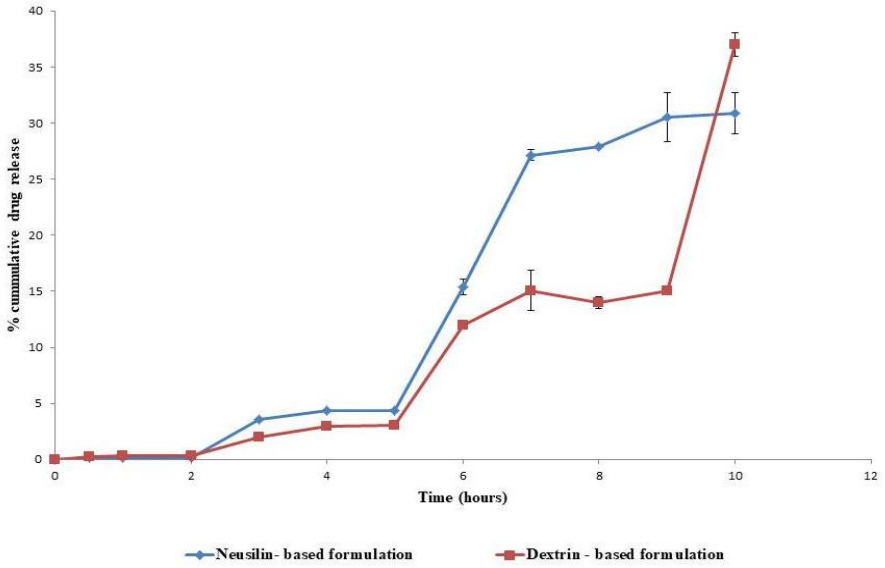


Figure 8. *In vitro* drug release of Neusilin and dextrin–based proniosomal formulations encapsulated in Eudragit FS 30D coated capsules.

4. Conclusions

Ciprofloxacin-loaded proniosomes formulations were successfully prepared by the slurry method with two carriers and various surfactant-to-cholesterol ratios. The formulated proniosomes possessed good *in vitro* characteristics, which include good flow properties, high entrapment efficiency (>80 %), smooth surface, and nano-sized particles. The Eudragit FS 30D coated capsules (containing ciprofloxacin proniosomes) showed negligible release in pH 1.2 and 6.8, but higher drug release occurred in pH 7.4, suggesting that colon-targeted release was achieved. The Eudragit® FS 30D coated capsules containing ciprofloxacin proniosome are a promising approach to sustain the release of ciprofloxacin, an antibiotic, for an extended period in the colon for the improved management of IBD. This study focused only on the *in vitro* characteristics of the colon-targeted ciprofloxacin vesicular system. The interesting results obtained in this study will guide further investigations on the effectiveness of this formulation on *in vivo* and *ex vivo* models.

Author Contributions

All authors have read and agreed to the published version of the manuscript.

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Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Piri-Gharaghie, T.; Ghajari, G.; Hassanpoor, M.; Jegargoshe-Shirin, N.; Soosanirad, M.; Khayati, S.; Farhadi-Biregani, A.; Mirzaei, A. Investigation of antibacterial and anticancer effects of novel niosomal formulated Persian Gulf Sea cucumber extracts. *Heliyon* **2023**, *9*, e14149, https://doi.org/10.1016/j.heliyon.2023.e14149.
2. Amandi, A.F.; Jokar, E.; Eslami, M.; Dadashpour, M.; Rezaie, M.; Yazdani, Y.; Nejati, B. Enhanced anti-cancer effect of artemisinin- and curcumin-loaded niosomal nanoparticles against human colon cancer cells. *Med. Oncol.* **2023**, *40*, 170, http://doi.org/10.1007/s12032-023-02032-7.
3. Ahasanuzzaman; Panner, S.R.; Pandey, A.K.; Chandy, V. Recent Trends in Niosomal Formulations for the Enhancement of Bioavailability. *Int. J. Pharm. Pharm. Res.* **2022**, *4*, 271–289.
4. Okore, V.C.; Attama, A.A.; Ofokansi, K.C.; Esimone, C.O.; Onuigbo, E.B. Formulation and Evaluation of Niosomes. *Indian J. Pharm. Sci.* **2011**, *73*, 323-328.
5. Mbah, C.C.; Attama, A.A.; Chapter 12 - Vesicular carriers as innovative nanodrug delivery formulations. In Organic Materials as Smart Nanocarriers for Drug Delivery; William Andrew Publishing: **2018**, 519-559, https://doi.org/10.1016/B978-0-12-813663-8.00012-9.
6. Rao, B.N.; Reddy, K.R.; Mounika, B.; Fathima, S.R.; Tejaswini, A. Vesicular Drug Delivery System: A Review. *Int. J. ChemTech. Res.* **2019**, *12*, 39–53, http://doi.org/10.20902/IJCTR.2019.120505.
7. Bhargava, T.; Dashora, K.; Rathore, U.; Panwar, S.; Bhargava, T.; Mandoria, N. A review on more stable niosome 'proniosomes' suitable carrier for TDDS. *J. Med. Care Res. Rev*. **2023**, *6*, 1278–1286.
8. Sakdiset, P.; Arce Jr., F.; See, G.L.; Sawatdee, S.; Yoon, A.S. Preparation and characterization of lidocaine HCl-loaded proniosome gels with skin penetration enhancers. *J. Drug Deliv. Sci. Technol.* **2023**, *86*, 104639, https://doi.org/10.1016/j.jddst.2023.104639.
9. Barani, M.; Sangiovanni, E.; Angarano, M.; Rajizadeh, M.A.; Mehrabani, M.; Piazza, S.; Gangadharappa, H.V.; Pardakhty, A.; Mehrbani, M.; Dell'Agli, M.; Nematollahi, M.H. Phytosomes as Innovative Delivery Systems for Phytochemicals: A Comprehensive Review of Literature. *Int. J. Nanomed.* **2021**, *16*, 6983–7022, http://doi.org/10.2147/IJN.S318416
10. Attama, A.A.; Momoh, M.A.; Builders, P.F. Lipid Nanoparticulate Drug Delivery Systems: A Revolution in Dosage Form Design and Development. In Recent Advances in Novel Drug Carrier Systems, Sezer, A.D., Eds.; *InTech*, **2012**, 107-140, http://doi.org/10.5772/50486.
11. Nasr, A.M.; Elhady, S.S.; Swidan, S.A.; Badawi, N.M. Celecoxib Loaded In-Situ Provesicular Powder and Its In-Vitro Cytotoxic Effect for Cancer Therapy: Fabrication, Characterization, Optimization and Pharmacokinetic Evaluation. *Pharmaceutics* **2020**, *12*, 1157, http://doi.org/10.3390/pharmaceutics12121157.

12. Rahman, S.A.; Abdelmalak, N.S.; Badawi, A.; Elbayoumy, T.; Sabry, N.; El Ramly, A. Formulation of tretinoin-loaded topical proniosomes for treatment of acne: *in-vitro* characterization, skin irritation test and comparative clinical study. *Drug Deliv.* **2015**, *22*, 731–739, http://doi.org/10.3109/10717544.2014.896428.
13. Patel, P.; Patel, K.S. PRONIOSOMAL CLOZAPINE TABLET: FORMULATION, EVALUATION OF PRONIOSOMAL TABLET AND RELEASE STUDY OF TABLETS. *Eur. Chem. Bull.* **2023**, *12*,3730–3737.
14. Gazzaniga, A.; Moutaharrik, S.; Filippin, I.; Foppoli, A.; Palugan, L.; Maroni, A.; Cerea, M. Time-Based Formulation Strategies for Colon Drug Delivery. *Pharmaceutics* **2022**, *14*, 2762, https://doi.org/10.3390/pharmaceutics14122762.
15. McCoubrey, L.E.; Favaron, A.; Awad, A.; Orlu, M.; Gaisford, S.; Basit, A.W. Colonic drug delivery: Formulating the next generation of colon-targeted therapeutics. *J. Control. Release* **2023**, *353*, 1107–1126, https://doi.org/10.1016/j.jconrel.2022.12.029.
16. Patel, S.; Bhadoria, A.; Patani, P. Colon targeted drug delivery systems: Based on Polymers. *J. Pharm. Negat. Results* **2022**, *13*, 1980–1988, https://doi.org/10.47750/pnr.2022.13.S03.295.
17. Ledder, O. Antibiotics in inflammatory bowel diseases: do we know what we're doing? *Transl. Pediatr.* **2019**, *8*, 42, http://doi.org/10.21037/tp.2018.11.02.
18. Mirzaie, A.; Peirovi, N.; Akbarzadeh, I.; Moghtaderi, M.; Heidari, F.; Yeganeh, F.E.; Noorbazargan, H.; Mirzazadeh, S.; Bakhtiari, R. Preparation and optimization of ciprofloxacin encapsulated niosomes: A new approach for enhanced antibacterial activity, biofilm inhibition and reduced antibiotic resistance in ciprofloxacin-resistant methicillin-resistance *Staphylococcus aureus*. *Bioorg. Chem.* **2020**, *103*, 104231, http://doi.org/10.1016/j.bioorg.2020.104231.
19. Yang, C.; Merlin, D. Nanoparticle-Mediated Drug Delivery Systems For The Treatment Of IBD : Current Perspectives. *Int. J. Nanomedicine* **2019**, *14*, 8875–8889, http://doi.org/10.2147/IJN.S210315.
20. Chen, F.; Liu, Q.; Xiong, Y.; Xu, L. Current Strategies and Potential Prospects of Nanomedicine-Mediated Therapy in Inflammatory Bowel Disease. *Int J Nanomedicine* **2021**, *16*, 4225–4237, http://doi.org/10.2147/IJN.S310952.
21. Wang, C.-P.J.; Byun, M.J.; Kim, S.-N.; Park, W.; Park, H.H.; Kim, T.-H.; Lee, J.S.; Park, C.G. Biomaterials as therapeutic drug carriers for inflammatory bowel disease treatment. *J. Control. Release* **2022**, *345*, 1–19, http://doi.org/10.1016/j.jconrel.2022.02.028.
22. Ugorji, O.L.; Umeh, O.N.C.; Agubata, C.O.; Adah, D.; Obitte, N.C.; Chukwu, A. The effect of noisome preparation methods in encapsulating 5- fluorouracil and real time cell assay against HCT-116 colon cancer cell line. *Heliyon* **2022**, *8*, e12369, https://doi.org/10.1016/j.heliyon.2022.e12369.
23. Onuigbo, E.; Nnamani, P.; Attama, A.; Okore, V.; Onuoha, E.; Ngene, A.; Esimone, C. Evaluation of DOTAP liposomes as vaccine adjuvant: Formulation, in-vitro characterization and stability. Proceedings of the 1st African International Conference/Workshop on Applications of Nanotechnology to Energy, Health and Environment, UNN, March 23-29, **2014**, pp 247 -261.
24. Mbah, C.C.; Builders, P.F.; Akuodor, G.C.; Kunle, O.O. Pharmaceutical Characterization of Aqueous Stem Bark Extract of *Bridelia ferruginea* Benth (Euphorbiaceae). *Trop. J. Pharm. Res.* **2012**, *11*, 637–644, http://doi.org/10.4314/tjpr.v11i4.15.
25. Carter, S.J. Powder Flow and Compaction. In: Cooper and Gun's Tutorial Pharmacy, Carter, S.J., Eds.; CBS Publishers and Distributors: India, **1986**, 186-232.
26. Aulton, M.E. Pharmaceutics: The Science of Dosage Form Design 2nd Edition. Churchill Livingstone, Edinburgh, **1999**; 1-734.
27. Raja, K.; Ukken, J.P.; Athul, P.V.; Sengodan, T.; Sivakumar, T. Formulation and evaluation of maltodextrin based proniosomal drug delivry system containing anti-diabetic (Glipizide) drug. *Int. J. PharmTech. Res.* **2011**, *3*, 471-477.
28. Mittal, S.; Chaudhary, A.; Chaudhary, A.; Kumar, A. Proniosomes : the effective and efficient drug-carrier system. *Ther. Deliv.* **2020**, *11*, 125-137, http://doi.org/10.4155/tde-2019-0065.
29. Ugorji, O.L.; Okoye, O.I.; Nwangwu, C.; Agbo, C.P.; Kenechukwu, F.C. Soluplus-stabilized 5-fluorouracil-entrappedniosomal formulations prepared via active and passive loading techniques: comparative physico-chemical evaluation. *J. Dispers. Sci. Technol.* **2023**, 1–9, https://doi.org/10.1080/01932691.2023.2186427.
30. Mousazadeh, N.; Gharbavi, M.; Rashidzadeh, H.; Nosrati, H.; Danafar, H.; Johari, B. Anticancer evaluation of methotrexate and curcumin coencapsulated niosomes against colorectal cancer cell line. *Nanomedicine* **2022**, *17*, 201-217, http://doi.org/10.2217/nnm-2021-0334.
31. Obitte, N.C.; Ofokansi, K.C.; Kenechukwu, F.C. Development and Evaluation of Novel Self-Nanoemulsifying Drug Delivery Systems Based on a Homolipid from *Capra hircus* and Its Admixtures

with Melon Oil for the Delivery of Indomethacin. *J. Pharm.* **2014**, *2014*, 340486, http://doi.org/10.1155/2014/340486.
32. Sezgin-Bayindir, Z.; Antep, M.N.; Yuksel, N. Development and Characterization of Mixed Niosomes for Oral Delivery Using Candesartan Cilexetil as a Model Poorly Water-Soluble Drug. *AAPS PharmSciTech* **2014**, *16*, 108–117, http://doi.org/10.1208/s12249-014-0213-9.
33. Obitte, N.C.; Ofokansi, K.; Chime, S.A.; Idike, E. Solid self-emulsifying drug delivery system based on a homolipid and vegetable oil: A potential vehicle for the delivery of indomethacin a disadvantaged drug. *Int. J. Green Pharm.* **2013**, *7*, 244–251.
34. Obitte, N.; Ugorji, L.; Ezichi, L.; Ogbodo, S.; Onyishi, V.; Chukwu, A. Ibuprofen self-emulsifying drug delivery system. *World J. Pharm. Pharm. Sci.* **2015**, *4*, 887–899.
35. Amol, S.S.; Mahendra, S.; Rajendra, C.D. Studies on Release Performance of Proniosmes and its Tablets of BCS Class II Drug Simvastatin. *Der Pharm Lettre* **2018**, *10*, 45–56. https://doi.org/10.1016/j.lwt.2020.110127.
36. Shruthi, P.A.; Pushpadass, H.A.; Franklin, M.E.E.; Battula, S.N.; Naik, N.L. Resveratrol-loaded proniosomes: Formulation, characterization and fortification. *LWT* **2020**, *134*, 110127, https://doi.org/10.1016/j.lwt.2020.110127.
37. Durgapal, S.; Mukhopadhyay, S.; Goswami, L. PREPARATION, CHARACTERIZATION AND EVALUATION OF FLOATING MICROPARTICLES OF CIPROFLOXACIN. *Int. J. Appl. Pharm.* **2016**, *9*, 1–8, http://doi.org/10.22159/IJAP.2017V9I1.14183.
38. Predoi, D.; Iconaru, S.-L.; Predoi, M.-V.; Buton, N. Development of Novel Tetracycline and Ciprofloxacin Loaded Silver Doped Hydroxyapatite Suspensions for Biomedical Applications. *Antibiotics* **2023**, *12*, 74, http://doi.org/10.3390/antibiotics12010074.
39. Hosseinpourpia, R.; Echart, A.S.; Adamopoulos, S.; Gabilondo, N.; Eceiza, A. Modification of Pea Starch and Dextrin Polymers with Isocyanate Functional Groups. *Polymers* **2018**, *10*, 939, http://doi.org/10.3390/polym10090939.
40. Neusilin Bronchure. Fuji chemical industry co. Ltd. Available online: http://harke.com/file admin/images/pharma/fuji_Neusilin. 2009. (Accessed 08 June **2023**).
41. Sahoo, S.; Chakraborti, C.K.; Naik, S.; Mishra, S.C.; Nanda, U.N. Structural Analysis of Ciprofloxacin-Carbopol Polymeric Composites by X-Ray Diffraction and Fourier Transform Infra-Red Spectroscopy. *Trop. J. Pharm. Res.* **2011**, *10*, http://doi.org/10.4314/tjpr.v10i3.14.
42. Naeem, M.; Choi, M.; Cao, J.; Lee, Y.; Ikram, M.; Yoon, S.; Lee, J.; Moon, H.R.; Kim, M.; Jung, Y.; Yoo, J. Colon-targeted delivery of budesonide using dual pH- and time-dependent polymeric nanoparticles for colitis therapy. *Drug Des. Devel. Ther.* **2015**, *9*, 3789–3799, http://doi.org/10.2147/DDDT.S88672.
43. Moghimipour, E.; Rezaei, M.; Kouchak, M.; Fatahiasl, J.; Angali, K.A.; Ramezani, Z.; Amini, M.; Dorkoosh, F.A.; Handali, S. Effects of coating layer and release medium on release profile from coated capsules with Eudragit FS 30D: an *in vitro* and *in vivo* study. *Drug Dev. Ind. Pharm.* **2018**, *44*, 861-867, http://doi.org/10.1080/03639045.2017.1415927.
44. Gonçalves, C.; Moreira, S.M.; Carvalho, V.; Silva, D.M.; Gama, M. Dextrin. In Encyclopedia of Biomedical Polymers and Polymeric Biomaterials, CRC Press: New York, **2016**; 2634–2649, http://doi.org/10.1081/E-EBPP-120050698.

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