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Effect of Different Polymers on Release of Nanoparticle Loaded Capsules of an Anti-Hyperlipidemic Drug

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ABSTRACT

This study aimed to develop nanoparticles of Rosuvastatin filled in capsules after the addition of sustained-release polymers to improve its bioavailability by increasing its lymphatic uptake. The nanostructured lipid carrier of Rosuvastatin was prepared using a high shear and ultrasonication method. 3% of Mannitol was added to the nano-suspension as a cryoprotectant. The freeze-dried nanoparticles were then filled in hard gelatin capsules, to which polyol, carbopol, novel polymers were added in two ratios (5, 10% w/w). capsules were evaluated for drug content, weight variation, and *in-vitro* release. The *in-vitro* release from the prepared capsules was 0.1 N HCl for 2 hrs and at phosphate buffer for another 22 hrs. The stability of capsules stored for three months. The resultant nanoparticle size was 42.98 (nm) with an entrapment efficiency of 78.86 %. Powder blends were exhibiting good flow properties. The *in-vitro* drug release from the investigated capsules showed the sustained release of the drug for 24 hrs. capsules chosen for stability gave minimal changes in drug content.

INTRODUCTION

Among the benefits which oral lipid-based formulations can provide are included: improvement and reduction in the variability of GI absorption of poorly water-soluble, lipophilic drugs. Different types of oral lipid-based formulations are like single-component lipid solutions, self-emulsifying formulations, self-emulsifying solid dispersion formulations and melt pelletization. It has been revealed that the most frequently chosen excipients for preparing oral lipid-based formulations were dietary oils composed of medium or long-chain triglycerides, lipid-soluble solvents, and various pharmaceutically-acceptable surfactants (Cremophor® EL, various Labrafil®, Labrasol®, and Gelucire®) ***(Mukherjee, S., et al., 2009).*** Since most of the drugs are available as solids and the stability of drugs is high at solid-state, solid oral drug delivery systems are the most popular category of oral drug delivery systems among pharmaceutical scientists who explore the use of different delivery systems for patient use. One of the most profound needs is to maintain drug concentration in systemic circulation for a longer period. This is one of the most desirable properties of an ideal drug delivery system. For, it reduces the frequency of administration and reduces the toxic effects of the drug. This objective can be achieved by formulating the drug in the controlled release dosage form. Advantages of hard gelatin capsule are their elongated shape, are easy to swallow, the flexibility of formulation. However, the biggest formulation advantage of capsules is that there is less need for additional excipients. Since capsules are tasteless, they effectively mask any unpleasant taste or odor of their contents (*Srividya, B., et al., 2014).*

Rosuvastatin is an anti-hyperlipidemic drug that exhibits low solubility and low bioavailability. It is used as the model drug for this study.

MATERIALS AND METHODS:

Rosuvastatin was kindly supplied by chemi- pharm, (**Egypt**). April CG, Maine, Labrasol ALF, and Transcutol HP were free samples kindly supplied by Gatefosse, (**France**). Carbopol 71 G and Noveon were kindly supplied by Lubrizol Advanced Materials, Inc., (**Cleveland, OH**). Polyox was kindly supplied by Colorcon Limited, Dartford Kent, (**UK**).

Preparation of nanosuspension containing Rosuvastatin loaded nanostructured lipid

Nanostructured lipid carriers of Rosuvastatin were prepared using high-speed homogenization with ultrasonication method, Briefly, 72 mg of Apifil (solid lipid) and 8 mg of Maisine (liquid lipid) melted on a water bath at 85 ^{o}C. To this lipid melt, 5 mg of Rosuvastatin was added to obtain a clear melting solution. An aqueous phase was prepared by dissolving 490 mg of Labrasol ALF as a surfactant and 210 mg of Transcutol HP as co-surfactant in 20 ml of distilled water and heated to the same temperature as that of the liquid lipid phase (***Gowda, D. V., et al., 2016***). This aqueous solution was poured into drug lipid mixture and homogenized using Ultra-Turrax® T18 basic homogenizer, IKA, (Germany) at 18000 rpm for 10 minutes, then sonicated for 15 minutes.

Determination of Entrapment Efficiency

The entrapment efficiency was determined by measuring the concentration of free drug in the aqueous phase. Nanoparticle dispersion was centrifuged at 15,000 rpm for 15 min to separate the lipid phase from the aqueous phase (***Kamble, S. S., et al., 2015***). After centrifugation, the supernatant was analyzed for the amount of un-entrapped drug by measuring absorbance at λ_{max} of 240 nm. Entrapment efficiency can be calculated using this equation:

$$\%EE = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Determination of particle size, poly dispersibility index

The particle size measurements were analyzed by dynamic light scattering using a Zetasizer NS 3000 (Malvern Instruments, Malvern, United Kingdom). The mean particle size and the polydispersity index (PDI) of NLCs in dispersion were measured at a scattering angle of 90° and a temperature of 25°C. Before the measurements, the dispersions were diluted with deionized water to an adequate scattering intensity (***Bhagawati, S. T., and Varsha N. S., 2017***).

Freeze-drying of the prepared nanoparticles

3 % w/v of mannitol was added to the nanodispersion before freezing (***Patel, R. J., and Patel, Z. P., 2013***). The dispersions were spread in a large petri-dish and kept in the deep freeze at -80^{o} C for 20 hours. Thin frozen films were obtained and were subjected to freeze-drying in a

lyophilizer (VirTis, SP Scientific) at -60° C and a pressure of 0.01 bar for 6 h. The obtained freeze-dried NLC was stored at 4^{o} C for further evaluations.

Preparation of Capsules containing Rosuvastatin loaded NLC

Rosuvastatin loaded NLC equivalent to 5 mg of Rosuvastatin calcium was weighed and physically blended with different polymers in two ratios in a glass mortar. 5 and 10% (w/w) of carbopol 71 G, noveon and polyox were used as the sustained polymers. The drug, polymers and other excipients were mixed geometrically and filled manually into the empty capsule shells. The composition of different capsules is given in table (1).

Compatibility study of Rosuvastatin loaded NLC with the added polymers Fourier-Transform Infrared Spectroscopy (FTIR):

A drug–excipient interaction plays a vital role in the release of drug from the formulation. Fourier transforms infrared (FTIR) spectroscopy has been used to compatibility between drugs and excipients. Samples of 1-2 mg of Rosuvastatin, Rosuvastatin loaded NLC, polymers and their physical mixture were studied using a Shimadzu FTIR 8300 spectrophotometer. They were mixed with KBr IR (grade) and compressed into discs in the compression unit under vacuum and scanned from 400-4000 cm^{-1} with an empty pellet holder as a reference ***(Ryakala et al., 2015)***.

Differential Scanning Calorimetry study (DSC):

Differential Scanning Calorimetry (DSC) study was also carried out to check drug–excipient compatibility. Approximately 5 mg of the aforementioned samples were weighed and placed in the aluminum pans and heated at a rate of 10^{o}C/min, with indium in the reference pan; in an atmosphere of nitrogen ***(Ahsan et al., 2015)***.

Micromeritics of powder

Bulk and tapped densities of powder were separately determined using a 10 mL measuring cylinder and after 500 tappings on a horizontal surface, respectively. Hausner's quotient and compressibility index were calculated from the two densities. The fixed-height funnel method was used to determine the flow rate and angle of repose. Briefly, time taken for ~20 g powder mass to flow through a funnel orifice height of 7.5 cm was recorded in g/s. The mean height of the powder peak and base diameter were calculated to obtain the angle of repose as the

ratio of powder height to the radius of the powder base. Triplicate measurements were carried out to ensure the validity of the result.

Table No. 1: Composition of different capsules containing Rosuvastatin loaded nanostructured lipid carrier

Formulae	Rosuvastatin (NLC) mg	Polyox (mg)	Carbopol 71 G (mg)	Noveon (mg)	talc	Mannitol (mg)
NLCC1	700	40			19	To 800
NLCC2	700	80			19	
NLCC3	700		40		19	
NLCC4	700		80		19	
NLCC5	700			40	19	
NLCC6	700			80	19	

1- Evaluation of capsules:

The prepared capsules were evaluated for weight variation, uniformity of content, dissolution studies, and kinetics of drug release.

Evaluation of capsules

Weight Variation

The capsules containing Rosuvastatin-loaded NLC were evaluated for weight variation. The weight of 20 empty capsules was determined individually. Then the mean weight of capsules was determined and hence weight variations can be obtained. Two capsules shouldn't deviate by 10% and none should deviate by 20% (***Aboul-Einien, M. H., et al, 2012***).

Uniformity of content

Contents of 10 capsules were weighed and removed. An amount equivalent to 5 mg of drug was dissolved in 100 ml methanol. Drug content was detected by measuring the absorbance at λmax 240 nm ***(Umair, W.T., and Ahmad, K. N., 2019)***.

Dissolution Studies

Drug release studies were carried out using a modified dialysis membrane technique. capsules were placed in a pre-soaked cellulose membrane which filled with 5 ml HCl, sealed and suspended in dissolution vessel (apparatus I). the dissolution flasks containing 900 ml of 0.1 N HCl for 2 hrs then replaced with phosphate buffer. The dissolution medium was maintained at a temperature of 37± 0.5 ºC with a constant speed of 75 rpm throughout the experiment for 24 hrs. 5ml samples were withdrawn at a predetermined interval and replaced with fresh medium. the percentage of drug release was calculated from the values of absorbances using the calibration curve ().

Kinetics of Drug Release

The dissolution profile of all the batches were fitted to zero-order kinetics, first-order kinetics, Higuchi, Hixon-Crowell, Korsmeyer and Peppas equation to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best fit model (***Supriya, A., et al., 2018***).

Short-term stability study

Capsules containing Rosuvastatin-loaded nanoparticle, NLCC1 and NLCC3 were subjected to two elevated temperatures, 35 and 45 ºC with a relative humidity of 75 % for accelerated stability testing for 3 months. Samples were taken at predetermined time intervals of 0, 15, 30, 60, and 90 days and evaluated for their drug content (***Shah, P., et al., 2015***).

RESULTS AND DISCUSSION

Entrapment efficiency, Particle size, and poly-dispersibility index

NLC-loaded Rosuvastatin showed 78.86 ± 4.16 % E.E. The particle size of the prepared formulae was 42.98 ±2.64 (nm) with PDI of 0.315. Maisine oil influenced the crystallization behavior and crystal structure of solid lipids so that high drug accommodation in the nano-particles was obtained. Also, the liquid oil content decreases the viscosity of the preparation and result in small particle size with homogeneity of its distribution.

Fourier- Transform Infrared Spectroscopy (FTIR):

The compatibility of Rosuvastatin with the polymers was confirmed by FTIR spectroscopy. The FT-IR spectrum of Rosuvastatin calcium powder was shown in figure (32-a). The results reveal identical spectra for the tested powder and the reference. Where a Characteristic peak of 2966.52 cm^{-1} is for N-H stretching. The other principle peaks are at 1543.05 cm^{-1} for C=C stretching, 3410.15cm^{-1} for a strong and broadband for O-H stretching,1433.90 cm^{-1} and 1381.03 cm^{-1} for asymmetric and symmetric bending vibration of CH3 group, respectively (***Ponnuraj R., et al., 2015***). The FT-IR spectrum of NLC is shown in figure (1-b) From the spectra, it was observed that there was no major shifting, as well as, no loss of functional peaks between the spectra of the drug, and drug-loaded NLC. There was a merge between hydroxyl groups of both Rosuvastatin and Apifil resulting in an intenser and a much broader band between 3290-3400. This indicated no interaction between the drug and the lipid. The intensity of other characteristic peaks of Rosuvastatin was found to be reduced in the ROS-NLC as seen in figure (1-b), which was mainly due to the molecular dispersion of crystalline Rosuvastatin in Apifil (***Agarwal, R., et al., 2015***).

FT-IR of polyox is demonstrated in figure (1-c), where the vibration bands around 2889.37 and 2858.51 cm^{-1} are due to the symmetric stretching and the asymmetric stretching of the methylene group. The strong vibration band around 1458.18 cm^{-1} is split into two bands and can be assigned to CH2 scissoring vibration bands. The 1342 cm^{-1} peak is related to the EO methylene wagging vibrations of the gauche conformation. the strong band around 1095.57 cm^{-1} can be assigned to the C–O–C stretching hydrated bond (***Calabrò, E., and Magazù, S., 2013***). Characteristic bands of carbopol were found at 3105 cm^{-1} (stretch absorption spectrum of O-H bond, and 1716.65 cm^{-1} (stretch absorption spectrum of C=O) (***Mei, L., et al., 2017***). Noveon AA-1 (figure 1-d) exhibits broadband at 1708.93 cm^{-1} assigned to C = O stretching (hydrogen-bonded). The weak band at 1411.89 cm^{-1} is due to the symmetric stretching of carboxylate anion (COO^{-}), bands 1242.16 and 1172.72 cm^{-1} are attributed to the C-O stretching ***(Pendekal, M. S. and Pramod, K. T., et al., 2012).*** The FTIR spectra of the physical mixture of Ros-loaded NLC with polyox, noveon (1-e), and carbopol revealed that there were no changes in major peaks of NLC indicating the compatibility of the drug and the used polymer.

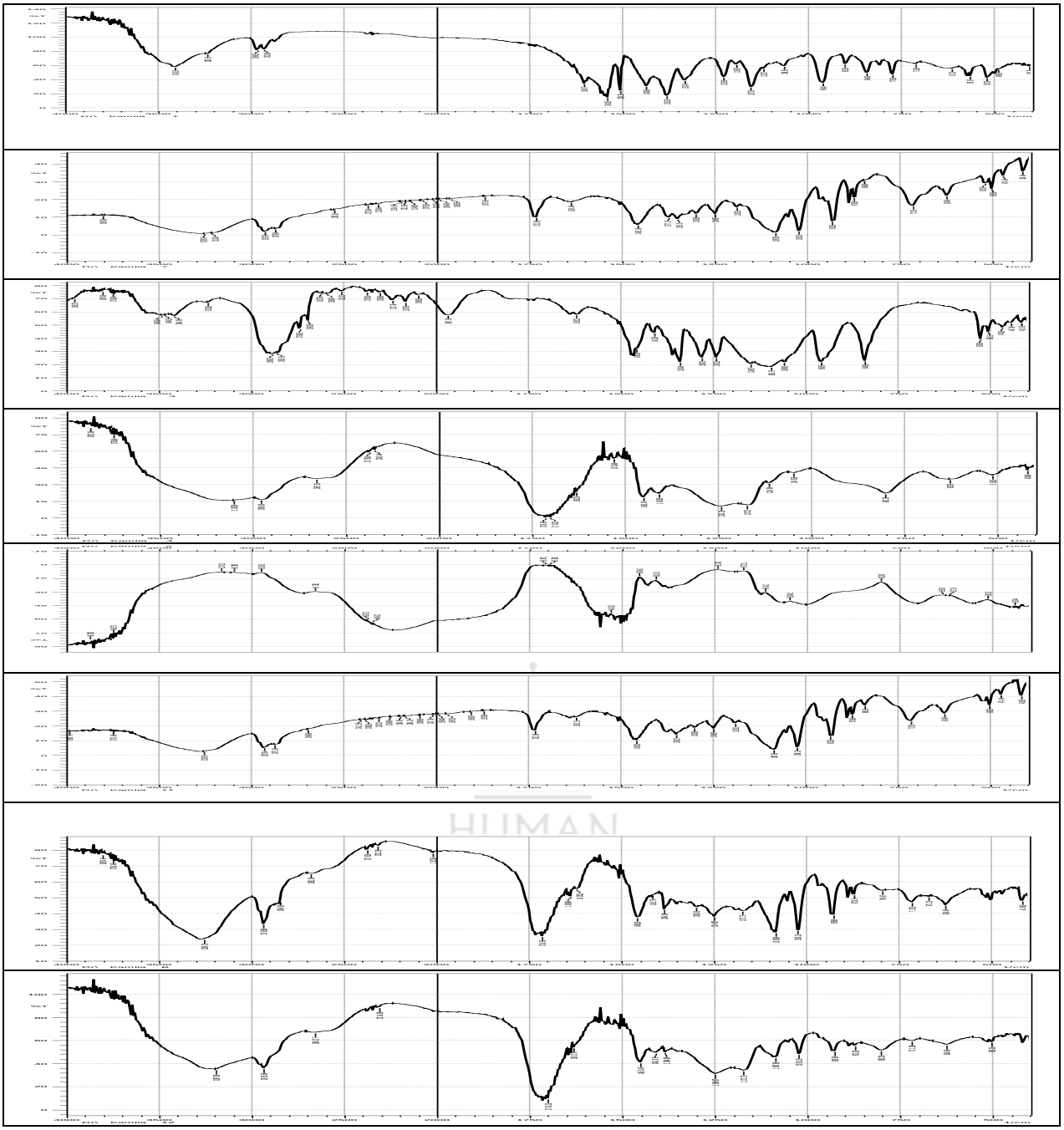

Figure No. 1: FTIR of (a) Rosuvastatin**, (b)NLC, (c) polyox, (d) carbopol (e) Noveon, (f) NLC and polyox physical mixture, (g) NLC and carbopol physical mixture and (h) NLC and Noveon physical mixture**

Differential Scanning Calorimetry (DSC):

The possible interactions between a lyophilized Rosuvastatin loaded NLC and other polymers used in capsules such as polyox, carbopol, and move on were determined by DSC. Pure Rosuvastatin in figure (2-a) shows two broad characteristic endothermic peaks at 85°C and

173°C this is because of the polymorphic forms of Rosuvastatin and it is a primary indication for crystalline nature of the pure drug. It also showed another endothermic peak at 238°C which corresponded to the degradation of Rosuvastatin ***(Ponnuraj, R., et al., 2015).*** The thermal behavior of NLC systems in figures (2-b) shows a shifting of the peak of Rosuvastatin in NLC from173 to 166.89 °C. It indicates that the crystalline nature of the drug gets completely converted into an amorphous form. Figure (2-c) illustrates the DSC thermogram of polyox that showed an endothermic peak at 73.65 °C, which is an indication of polyox melting point (***Jagdale, S. C., et al., 2014; Shojaee S., et al., 2015***). DSC thermogram of Carbopol in figure (2-d) showed a characteristic endotherm at 280 °C which corresponds to its melting point and another a broad endothermic peak near 100°C which was attributed to the evaporation of physically bound or absorbed water from the polymers during heating (***Karwa P., et al., 2013***). Polycarbophil (noveon) thermogram (2-e) exhibits two endothermic peaks at 80- 100 °C and ~245°C. The first endothermic peak is assigned to the evaporation of water from hydrophilic groups in the polymers and the second one corresponds to a thermal degradation through intermolecular anhydride formation and water elimination.

Figures (2-f, 2-g, and 2-h) represented thermograms of the physical mixture of Ros-loaded NLC with polyox, carbopol, and noveon respectively. The endothermic peak of Rosuvastatin was found in all thermograms indicating the compatibility of the drug nanoparticles with the used polymers.

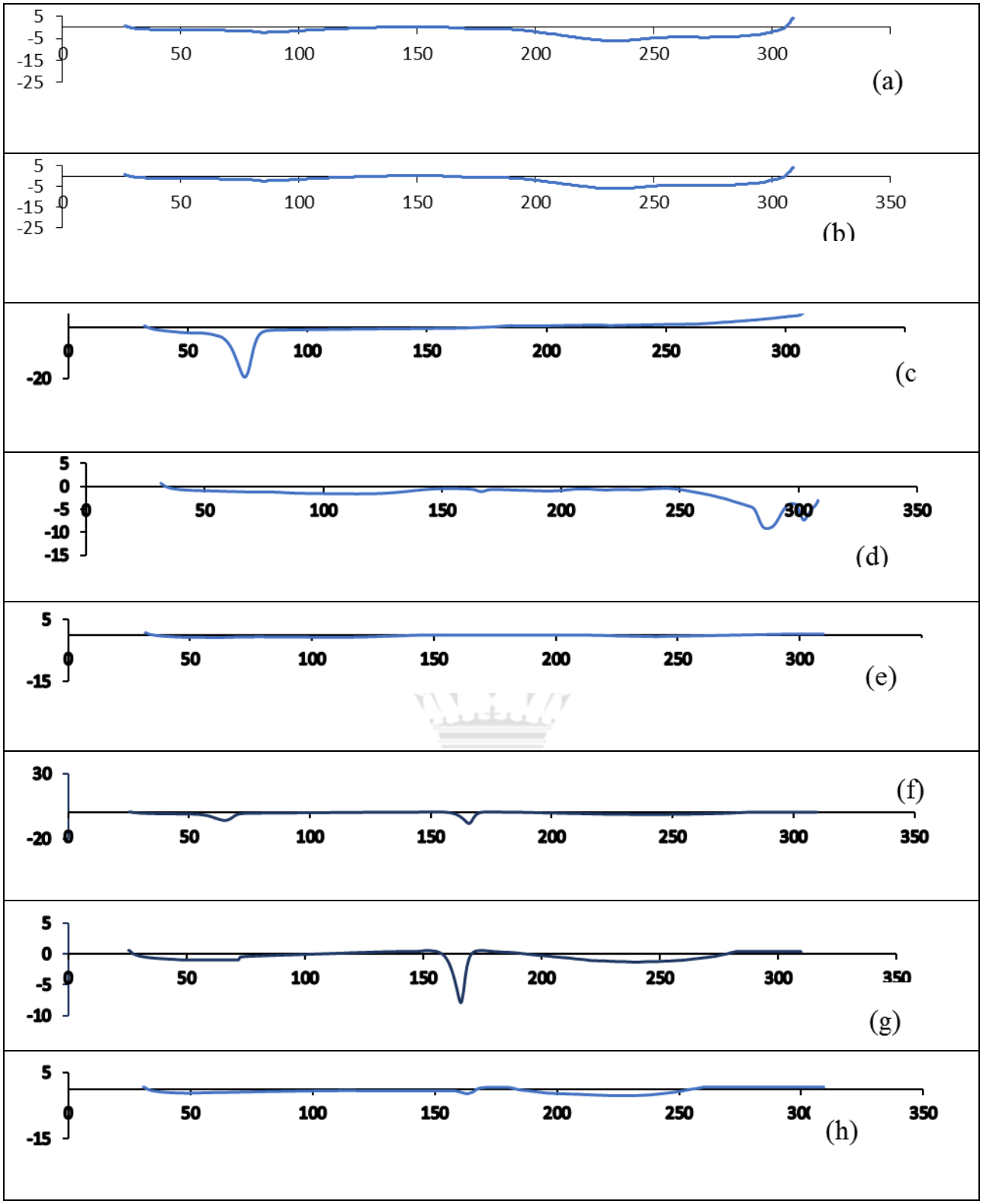

Figure No. 2: DSC OF (a) Rosuvastatin, (b)NLC, (c) polyox, (d) carbopol (e) Noveon, (f) NLC and polyox physical mixture, (g) NLC and carbopol physical mixture and (h) NLC and Noveon physical mixture

Micrometrics of powder

For flowability, the angle of repose and compressibility index was measured. Flow properties of the powder, as well as resistance to particle movement, can be judged from the angle of repose. This measurement gives a qualitative and quantitative assessment of the internal cohesive and frictional forces ***(Patil et al., 2011)***.

Regarding flowability, In NLC loaded powder blend, NLCC4 gave 31.22 which indicates excellent flow property. All other NLC loaded capsules exhibited values between (33.29-36.25) which indicates good and fair flow properties (Table 2).

Also, all Rosuvastatin loaded NLC powders gave Hausner's ratio values between (1.18- 1.24) which indicates good to fair flow properties as seen in the table (2). These parameters indicate good flow properties of all formulations and suitability for filling into capsules.

Table No. 2: Characterization of the prepared powder blend of capsules containing Rosuvastatin loaded NLC

formulae	The angle of Repose Φ	Bulk density (gm /ml)	Tapped density (gm /ml)	Hausner ratio	Carr′s index
NLCC1	38.25	0.69	0.85	1.23	6.153
NLCC2	37.11	0.73	0.89	1.22	7.594
NLCC3	35.01	0.75	0.90	1.20	6.25
NLCC4	31.22	0.78	0.92	1.18	4.878
NLCC5	34.92	0.78	0.93	1.19	18.072
NLCC6	35.41	0.75	0.93	1.24	6.578

Evaluation of capsules:

Weight variation

Weight variations of all nanoparticles loaded capsules were found to be within the limit (Table 3).

Table No. 3: Uniformity of weight of Rosuvastatin loaded nanoparticles capsules

Formulations	Weight (y)	Deviation (ỹ - y)	% Deviation
NLCC1	806.00	5.50	0.575
NLCC2	799.00	-2.13	0.225
NLCC3	804.00	1.40	0.147
NLCC4	801.00	-0.40	0.042
NLCC5	800.00	1.67	0.175
NLCC6	795.00	-6.43	0.681

Content uniformity

Table (4) show the content uniformity of all formulations. It was found that all capsules comply with the pharmacopoeial requirement regarding the content uniformity which is (90-110%) *(USP, 2011).* Drug content of all capsules ranged from 93.53 % to 104.82% indicating content uniformity in all formulation.

Table No. 4: Drug content of Rosuvastatin loaded nanoparticles capsules

Capsules	Drug content (Mean ± S.D.)
NLCC1	98.73 ± 4.02
NLCC2	96.07 ± 0.85
NLCC3	99.67 ± 3.51
NLCC4	95.83 ± 4.31
NLCC5	103.02 ± 2.01
NLCC6	93.53± 0.98

***In-vitro* drug release**

All capsules gave sustained drug release ranging from 74.75 % (NLCC6) to 100.24% (NLCC3) at 24 hr. This might be due to the effect of two parameters, the polymer type, and concentration. The first polymer used in these formulations is polyox (NLCC1, and NLCC2), which is well known for its swelling capacity that created long channels within the swollen matrix. This allowed the embedded drug to be released slowly into the media (***Chaudhari, S.P., et al., 2012***). The other two polymers used are carbopol (NLCC3, and NLCC4), and

noveon (NLCC5, and NLCC6), which are crosslinked acidic polymers (***López, Y.A.A., and Robles, L.V., 2016***) that swell faster in alkaline pH compared to acidic pH. Since each polymer particle is capable of forming a hydrogel, in which the drug is dispersed. Crosslinks enhance the ability of gel-particles to entrap the drug molecules, however, they absorb a lot of water and create osmotic pressure inside the gel. When fully hydrated, the osmotic pressure breaks up the structure and shed off individual pieces of hydrogels (***Mohamed, S. P, et al., 2011***). As the polymer concentration increased, the diffusion of Rosuvastatin through the formulation reduced as clearly seen in formulations NLCC2 (75.66%), NLCC4 (80.45%), and NLCC6 (74.75%), which gave slower rate of drug released when compared to NLCC1 (94.78%), NLCC3 (100.24%), and NLCC5 (84.40%), respectively. This might be due to the more entangled nature of the polymeric network. Besides, the ingress of water into the formulation containing a high concentration of polymer was reduced, thus lowering the rates of both dissolution and erosion (***Patel, P. B., et al., 2012***). Also, these channels in the hydrogel are dependent on the concentration of polymer, thus, polymer concentration, the extent of crosslinking, pH of the dissolution media can significantly influence the hydrogel properties hence drug release.

Comparatively, Rosuvastatin released from polyox (NLCC2) and carbopol (NLCC4) showed 75.66% and 80.45% release at 24 hr, respectively. This finding might be due to the higher swelling efficiency of polyox than carbopol that created longer channels within the swollen matrix (***Prabhu, S. et al., 2008).*** Formulations containing noveon NLCC5 and NLCC6 showed the lowest drug release (84.40%, and 74.75%, respectively) compared to formulations containing other polymers. This finding might be due to the less acidic nature of noveon which swells slower than carbopol 71G in basic media (***Mohamed S. P, et al., 2011***), which led to the slower rate of drug release.

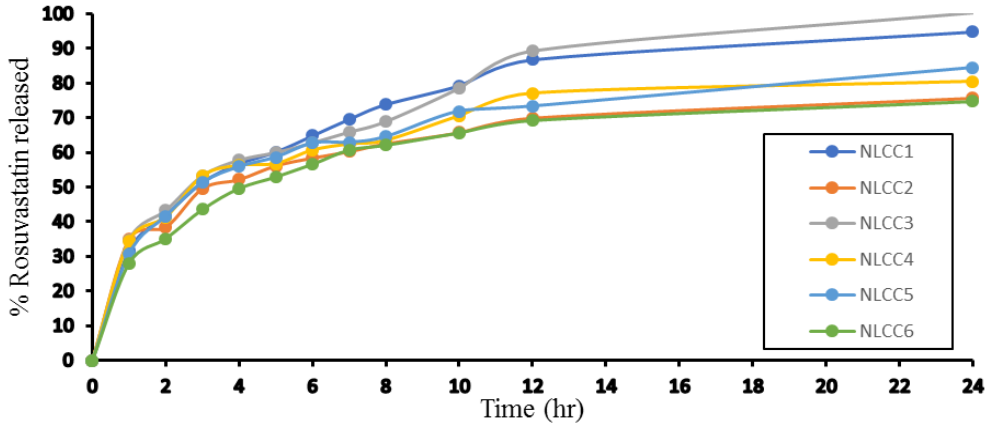

Figure No. 3: *In-vitro* drug release

Kinetic analysis of the dissolution data of Rosuvastatin from different SLNs and NLCs:

Table (5) shows the kinetic analysis of the *in-vitro* dissolution data of Ros from different capsules. According to the correlation coefficient (r), the *in-vitro* release data of all formulations followed second-order kinetics except SLNC2, SLNC6, NLCC7, and NLCC9 which followed diffusion-controlled release kinetics, therefore it can be concluded that the rate of drug release follows second order kinetics with diffusion-controlled release mechanism as per Higuchi model.

Table No. 5: Kinetic parameters calculated for the dissolution data of Rosuvastatin from different capsules containing nanoparticles

Formula	Model	a	b	r	k	$t_{(1/2)}$
NLCC1	zero	44.120	2.811	0.911	2.811	17.786
	First	2.400	-0.158	-0.936	-0.365	-1.900
	Second	-20.764	4.009	0.854	4.009	0.002
	Diffusion	19.419	18.045	**0.980**	18.045	7.677
NLCC2	zero	44.334	1.659	0.858	1.659	30.133
	First	1.756	-0.018	-0.924	-0.042	-16.465
	Second	0.016	0.001	**0.970**	0.001	8.799
	Diffusion	28.977	10.959	0.949	10.959	20.818
NLCC3	zero	45.110	2.616	0.911	2.616	19.116
	First	1.882	-0.058	-0.967	-0.134	-5.185
	Second	-0.036	0.013	0.939	0.013	0.792
	Diffusion	22.401	16.682	**0.973**	16.682	8.984
NLCC4	zero	45.970	1.841	0.857	1.841	27.154
	First	1.750	-0.023	-0.923	-0.052	-13.228
	Second	0.016	0.002	**0.958**	0.002	6.121
	Diffusion	29.014	12.127	0.945	12.127	17.000
NLCC5	zero	44.672	2.029	0.871	2.029	24.643
	First	1.772	-0.026	-0.965	-0.061	-11.368
	Second	0.013	0.002	**0.997**	0.002	4.744
	Diffusion	26.148	13.299	0.957	13.299	14.135
NLCC6	zero	40.433	1.876	0.837	1.876	26.650
	First	1.784	-0.019	-0.905	-0.045	-15.466
	Second	0.015	0.001	**0.958**	0.001	8.724
	Diffusion	22.644	12.559	0.938	12.559	15.851

Stability study

No changes in the drug content of the prepared capsules were observed throughout the storage period.

CONCLUSION

In this study, the low solubility of Rosuvastatin and hence its bioavailability was overcome through the development of nanostructured lipid carriers. nanoparticles of rosuvastatin calcium were successfully developed, lyophilized and incorporated into capsules with good flow properties. Physicochemical and pharmacokinetic properties of drugs can be enhanced by developing Sustained release formulations. It can be concluded that 5% (w/w) of carbopol 71G capsules are efficient in providing the sustained release of Rosuvastatin over 24 hours.

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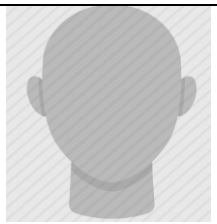	***Manal Kamal Mohammed Darwish*** *Professor of Pharmaceutics and Industrial Pharmacy.* *Department of Pharmaceutics and Industrial pharmacy, Faculty of Pharmacy, Al-Azhar University (Girls), Cairo, Egypt.*
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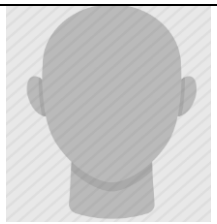	***Kamilia Hussien Abdelhady Mohammed–*** *Assistant lecturer in pharmaceutics, Pharmaceutics and industrial pharmacy department, Faculty of Pharmacy, Al-Azhar University. Cairo, Egypt.*