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Original research article

Formulation, Development and Evaluation of Praziquantel Loaded Nanosponges (PZQ-Nsgs) by Using Factorial Design

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Abstract:
Introduction: Praziquantel is used to treat diseases caused by infection with numerous types of internal/gastrointestinal and external parasites. **Aim:** The aim of this study was to design, formulate and evaluation of Praziquantel loaded nanosponges (PZQ-NSGs) by using factorial design. **Methodology:** The Determination of Calibration curve by UV visible spectrophotometer and Analytical method validation by UV visible spectrophotometer. The Analytical Techniques Used to Detect Drug-Excipient Compatibility of drug.
Results and Discussion: The developed nanosponge drug delivery system were subjected to stability testing at higher temperature and humidity condition i.e. at 40ºC ± 2ºC and RH 75% ± 5 % after 6 months as per ICH guidelines. Solid state characterization of freeze dried PZQ-NSGs have been done with FTIR, PXRD, particle size analysis. From above characterization it was observed that, the sample was remained stable at 40ºC ± 2ºC and RH 75% ± 5 % even after 6 months.
Conclusion: Formulated nanosponges formulation was found to be stable at accelerated stability conditions as per ICH guidelines up to 6 months. Nanosized distribution, amorphous nature, better encapsulation and inclusion complexation with EC were found to be the major drivers for significant improvement in solubility, nanosized particles, dissolution efficiency and stability.
Keywords: Praziquantel, nanosponges, Analytical techniques, CH guidelines, stability.

Introduction

Nanomaterials have a numeral of benefits as drug transporters. Nanocarriers can: i) enhance aqueous solubility and defend drugs dissolved in the systemic circulation, enhancing the pharmacokinetic and pharmacological traits of the actives; ii) target the liberation of actives in a tissue or cell-specific manner, thereby preventing the actives accumulation in the liver, kidneys, spleen, and other non-targeted organs and improving therapeutic effectiveness; and iii) transport a mixture of imaging and therapeutic agents for concurrent scrutinizing of therapeutic efficacy (Burgess P et al., 2010 and Farokhzad O et al., 2009). Every class of nanomaterials has exclusive pros and cones; thus, to reveal the rising possibilities of unlike

nanovectors for diverse therapeutic uses, their applicable molecular targets, and their benefits and limitations are to be imperative.

The development of a wide spectrum of nanoscale technologies is beginning to modify the foundations of disease diagnosis, treatment and prevention (Doshi N et al., 2009). A variety of nano devices have had a noteworthy impact on medical technology, to a great extent improving the efficacy of many existing actives and enabling the building of entirely new therapeutic modalities (Moghimi S et al., 2005). In current years, noteworthy efforts have been dedicated to utilize the prospectives of nanotechnology in drug delivery to widen an appropriate means of site-specific and/or time controlled delivery of minute or huge molecular weight actives and other bioactive cargo (Hamidi M et al., 2008). Research into the release and targeting of actives with nanosized particles is at the vanguard of projects in nanomedicine. Nanoparticles show tremendous promise for drug delivery, while exhibiting structural properties that are not feasible for single molecules (Sajja H et al., 2009). Polymeric nanoparticles, in meticulous, are the most commonly researched beneficial carriers due to their exclusive litheness with respect to invention techniques[1-4].

Complexing nanoparticles are nanoparticle that attracts the fragment by electrostatic charges and conjugating NPs are the nanoparticles that link the drug all the way through covalent bond. The innovation of NSGshas to turn out to be a noteworthy pace toward conquering these problems. A different chief nature of these sponges is their water solubility; this permits the utilization of these systems in tip of fact for drugs with low solubility. These petite sponges can travel around the body until they stumble upon the target location and fuse on the surface and began to discharge the actives in a controlled and conventional manner, which is more valuable for a meticulous given dosage. Owing to their minute size and porous nature, they can unite poorly-soluble drugs within their matrix and improve their bioavailability. As shown in Fig 2, a polymer core which enable to reveal the core structure. They can be crafted for targeting drugs to the definite site, put off drug and protein degradation and make longer the drug liberate in a controlled manner[5-7].

Praziquantel (PZQ) is a representative example of this above group. Schistosomiasis is a parasitic disease caused by blood flukes of the genus schistosoma, being a serious public health problem in < 70 countries of the tropics and subtropics without potable water and poor sanitary conditions. Praziquantel is used to treat diseases caused by infection with numerous types of internal/gastrointestinal and external parasites[8-11].

Methodology

- Determination of Calibration curve by UV visible spectrophotometer
- Analytical method validation by UV visible spectrophotometer
- Determination of melting point
- Drug stability study
- Saturation Solubility study
- Analytical Techniques Used to Detect Drug-Excipient Compatibility
- Differential Scanning Calorimetry (DSC):
- Non thermal Techniques or Spectroscopic techniques:
- FT-IR Spectroscopy (Vibrational spectroscopy)
- Powder X-ray diffraction (PXRD)
- Microscopic technique:
- Scanning electron microscopy (SEM)
- Thermal Technique:
- Differential Scanning Calorimetry (DSC)
- Non thermal Techniques or Spectroscopic techniques:
- FT-IR Spectroscopy (Vibrational spectroscopy):

Table 1: Design matrix of formulation

Step I: Synthesis of β-CD Nanosponges					
Ingredients	F1	F2	F3	F4	F5
β-CD:DMC (mmol or gm)	1:1	1:2	1:3	1:4	1:5
β-CD (gm)	17.42	17.42	17.42	17.42	17.42
β-CD (mmol)	15.34	15.34	15.34	15.34	15.34
DMC (gm)	9.96	19.92	29.88	39.84	49.8
DMC (mmol)	61.42	122.84	184.26	245.68	307.1
Ethanol (ml)	100	100	100	100	100
Step II: Preparation of PZQ-Loaded NS					
ATRC: β-CD (w/w)	1:1	1:2	1:3	1:4	1:5
Drug	20	20	20	20	20
β-CD NSGs	20	40	60	80	100
Dist. water (ml)	20	20	20	20	20
Centrifugation (RPM)	2000	2000	2000	2000	2000

Table 2: Design matrix of formulation

Step I: Synthesis of β-CD Nanosponges			
Ingredients	**F1**	**F2**	**F3**
DMF	100	100	100
β-CD:DMC (mmol or gm)	1:2	1:4	1:8
β-CD (gm)	17.42	17.42	17.42
β-CD (mmol)	15.34	15.34	15.34
DMC (gm)	19.92	39.84	79.68
DMC (mmol)	30.68	61.36	122.72
Ethanol (ml)	100	100	100
Dist. water (ml)	100	100	100
Step II: Preparation of PZQ-Loaded NS			
PZQ: β-CD (w/w)	1:5	1:10	1:15
β-CD NSGs	100	200	300
Dist. water (ml)	20	20	20
Centrifugation (RPM)	2000	2000	2000

Table 3: Design matrix of formulations

Ingds. Batches	**PZQ (mg)**	**DMSO (ml)**	**EC (mg)**	**β-CD (mg)**	**WPI (mg)**	**DMC (ml)**	**Dist. Water(ml)**	**Ethanol(ml)**
F1	20	10	500	500	100	46.3	150	100
F2	20	10	--	1000	100	46.3	150	100
F3	20	10	500	500	100	23.15	150	100
F4	20	10	500	500	100	46.3	150	100
F5	20	10	1000	--	100	46.3	150	100
F6	20	10	1000	1000	100	23.15	150	100
F7	20	10	500	500	100	23.15	150	100
F8	20	10	1000	1000	100	23.15	150	100

Table 4: Design matrix of formulations

Batches Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight of drug (mg)	20	20	20	20	20	20	20	20	20
PVA: EC (%w/w)	1:1			1:2			1:3		
WPI :EC (%w/w)		1:2			1:3			1:1	
SPI:EC (%w/w)			1:3			1:1			1:2
DCM (ml)	20	20	20						
GTAD (ml)				20	20	20			
DMC (ml)							20	20	20
DW (ml)	150	150	150	150	150	150	150	150	150

Table 5: Formulation of SLNs using factorial design

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
Weight of drug (mg)	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**
WPI :EC	**1:20**	**1:20**	**1:10**	**1:10**	**1:20**	**1:10**	**1:20**	**1:10**
(%w/w)								
DCM (ml)	10	20	10	20	10	10	20	20
DW (ml)	150	150	150	150	150	150	150	150
SS (RPM)	4000	500	500	4000	500	4000	4000	500

Table 6: Design matrix of Independent Variables

Batches	CODED LEVELS		
	X1 (mg)	X2 (mL)	X2(rpm)
F1	+1	-1	+1
F2	+1	+1	-1
F3	-1	-1	-1
F4	-1	+1	+1
F5	+1	-1	-1
F6	-1	-1	+1
F7	+1	+1	+1
F8	-1	+1	-1

Aim:

The aim of this study was to design, formulate and evaluation of Praziquantel loaded nanosponges (PZQ-NSGs) by using factorial design.

Objectives

- To fabricate the nanoporous drug delivery system of praziquantel for enhancement of solubility, better encapsulation, dissolution rate and oral therapeutic effectiveness.
- To explore its application in the improvement of bioavailability, sustained release/ controlled release preparations as well as stability enhancement.
- To investigate the influence of various experimental parameters on nanoparticles like type, concentration and molecular weight of cross linkers, drug concentration and process parameters of ultrasonication.
- To investigate the oral bioavailability of developed formulations by *in-vivo* pharmacodynamic study in animals.

Results

Table 7: FTIR Spectra Observed Frequencies of Praziquantel

Sr. No	Functional Group	Reported frequency(cm^{-1})	Observedfrequency(cm^{-1})
1	C=C bending strong	730-665	692.32
2	C=C bending strong	730-665	723.17
3	C-H bending strong	750 ± 20	765.6
4	C=C bending medium	840-790	829.24
5	C-Cl stretching strong	850-550	855.27
6	C=C bending alkene	895-885	892.88
7	C=C bending alkene	995-985	997.01
8	C-O stretching (Sec. alc)	1124-1087	1088.62
9	C-O stretching (Ter. alc)	1205-1124	1127.19
10	C-O stretching (Ester)	1210-1163	1211.08
11	C-O stretching (Aromatic ester)	1310-1250	1260.25
12	C-N stretching	1350-1300	1300.75
13	O-H bending	1390-1310	1327.64
14	O-H bending Alcohol	1420-1330	1421.2.8
15	C=O stretching (δ-lactam)	1650	1649.8
16	O-H stretching	3300-2500	2660.32
17	C-H stretching alkane	3000-2840	2853.17
18	N-H stretching strong, broad	3000-2800	2929.34
19	N-H stretching medium	3400-3300	3286.11

Table 8: Recovery studies

Sr. No	Level of % Recovery	Initial amount present (µg/ml)	Amount of Std. Added (µg/ml)	Total Amount present (µg/ml)	Total amount Recove red (µg/ml)	% Recovery	% Mean Recovery
1	80	10	8	18	17.90	99.46	99.97±0.4524
	80	10	8	18	18.02	100.11	
	80	10	8	18	18.06	100.33	
2	100	10	10	20	19.78	98.92	99.38±0.5575
	100	10	10	20	20.00	100.00	
	100	10	10	20	19.84	99.22	
3	120	10	12	22	21.86	99.38	99.73±0.3550
	120	10	12	22	21.94	99.73	
	120	10	12	22	22.02	100.09	

Table 9: Results of robustness

Solvent Composition	Drug in standardsolution (µg/ml)	Measured conc.(µg/ml)	% Recovery
0.1 N NaOH with2% Methanol	16	16.137	100.85
	16	15.98	99.877
	16	15.901	99.387
	MEAN (n=3±SD)	16.006±0.120	100.38±0.745
0.1 N NaOH	16	15.862	99.142
	16	15.823	98.897
	16	15.784	98.651
	MEAN (n=3±SD)	15.823±0.039	98.897±0.246

Table 10: Reported and observed IR frequencies of PZQ

Sr. No	Functional Group	Reported frequency(cm^{-1})	Observed frequency(cm^{-1})
1	C=C bending strong	730-665	692.32
2	C=C bending strong	730-665	723.17
3	C-H bending strong	750 ± 20	765.6
4	C=C bending medium	840-790	829.24
5	C-Cl stretching strong	850-550	855.27
6	C=C bending alkene	895-885	892.88
7	C=C bending alkene	995-985	997.01
8	C-O stretching (Sec. alc)	1124-1087	1088.62
9	C-O stretching (Ter. alc)	1205-1124	1127.19
10	C-O stretching (Ester)	1210-1163	1211.08
11	C-O stretching (Aromatic ester)	1310-1250	1260.25
12	O-NO_2, nitrates	1300-1250	1300.75
13	O-H bending	1390-1310	1327.64
14	O-H bending Alcohol	1420-1330	1421.28
15	C=O stretching (δ-lactam)	1650	1649.8
16	O-H stretching	3300-2500	2660.32
17	C-H stretching alkane	3000-2840	2853.17
18	N-H stretching strong, broad	3000-2800	2929.34
19	N-H stretching medium	3400-3300	3286.11

Table 11: Analysis of variance table for PS

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	112.53	4	28.13	21.32	0.0153	significant
X_1	28.72	1	28.72	21.76	0.0186	
X_1X_2	19.75	1	19.75	14.97	0.0306	
X_2X_3	12.95	1	12.95	9.81	0.0520	
$X_1X_2X_3$	51.10	1	51.10	38.72	0.0084	
Residual	3.96	3	1.32			
Cor Total	116.49	7				

Table 12: Analysis of variance table for % CDR

Source	Sum of Squares	df	Mean Square	F-value	p-value	Result
Model	9.42	6	1.57	1148.79	0.0226	Significant
A-EC	1.75	1	1.75	1283.31	0.0178	
C-SS	0.4487	1	0.4487	328.31	0.0351	
AB	0.1507	1	0.1507	110.28	0.0604	
AC	0.2036	1	0.2036	148.97	0.0520	
BC	0.0453	1	0.0453	33.18	0.1094	
ABC	6.82	1	6.82	4988.67	0.0090	
Residual	0.0014	1	0.0014			
Cor Total	9.42	7				

Table 13: Percent drug encapsulation and drug loading of NSGs[a]

Run	Percent drug Encapsulation (%)	Unentraped Drug (%)	Drug Loading (%)	Solubility (µg/ml)
F1	81.46±0.35	185.43±0.35	35.42±1.872	71.61±0.649
F2	86.33±1.73	136.70±1.73	37.53±1.325	76.72±0.511
F3	89.59±2.18	104.13±2.18	59.72±0.952	78.13±0.598
F4	90.12±0.35	98.80±0.35	60.08±2.941	101.47±1.228
F5	75.30±1.92	246.97±1.92	32.74±1.167	117.08±2.465
F6	**93.26±2.21**	**67.43±2.21**	**62.17±1.963**	**235.10±0.907**
F7	79.38±2.08	206.17±2.08	34.51±0.971	145.30±0.796
F8	87.13±2.89	128.70±2.89	58.09±1.624	156.98±5.579

Table 14: ^{1}H-NMR chemical shifts of PZQ-NSGs

δ values	Integration	Proton Type	Number
1.238 Multiplet	4.13	C-H	1
1.375, 1.372 Doublet	21.33	2XCH_3	6
1.361, 1.359 Doublet			
1.610, 1.689 Multiplet	3.18	CH_2	2
1.946, 1.930 Doublet	3.22		
2.047,2.039 Doublet	3.09, 3.06	H-C-H (CH_2)	2
3.228 Multiplet	3.49	C-H	1
3.646 Multiplet	3.81	CH_2	1
3.744, 3.736 Multiplet	6.15	CH_2 (N-CH_2)	2
3.948 Multiplet	3.20	C-H	1
6.980, 7.522 Multiplet	6.06, 11.89,18.37, 6.00	2 (H), 4H, 6H, 2H Aromatic C-H	14
9.838 Singlet	3.03	N-H	1

Table 15: Stability study of PZQ-NSGs

Time (Month/s)	Physical Appearance	Particle size (nm)	EntrapmentEfficiency (%)	% CDR	Solubility (µg/ml)
25±2ºC/65± 5% RH					
0	White crystalline powder	134.47±0.31	93.66±0.93	92.18	235.10±0.907
3	white crystalline powder	134.77±0.15	93.25±0.62	91.64	233.53±0.891
6	white crystalline powder	134.53±0.60	92.44±0.94	91.36	232.43±2.248
30±2ºC/70±5% RH					
0	white crystalline powder	134.93±0.15	92.03±2.68	92.46	234.76±0.130
3	white crystalline powder	134.87±0.35	91.00±1.27	91.91	234.54±0.233
6	White crystalline powder	135.03±0.31	90.39±1.28	91.77	233.74±0.844
40±2ºC/ 75±5% RH					
0	white crystalline powder	134.90±0.44	93.48±2.12	92.72	234.88±0.523
3	white crystalline powder	134.93±0.25	92.23±2.16	92.18	233.73±0.721
6	white crystalline powder	135.07±0.81	92.64±1.84	92.44	232.00±2.247

Discussion

Analytical processes are usually recognized as robust if percent recovery is within 98-102%. Moreover, in all tests, the found concentration of PZQ was between 100.38 ± 0.745% and 98.897 ± 0.246% of nominal value, as recommended by the United States Pharmacopoeia. PZQ presents the most relevant assignments were one small peaks at 3286.11 cm^{-1} N-H stretching medium and two strong sharp intense peaks at 2929.34 cm^{-1} and 2853.17 (stretching of C–H bound to tertiary amines in the lactam ring); one strong peaks at 2660.32 cm^{-1} (O-H stretching); C=O stretching (δ-lactam) at 1649.8 cm^{-1}, a strong band O-H bending Alcohol at 1421.2.8 cm^{-1}, centered at 1327.64 cm^{-1} (O-H bending); a strong band centered around 1300.75 cm^{-1} (O-NO2, nitrates); and a peak at 1260.25 cm^{-1} (C-O stretching (Aromatic ester). Ethyl cellulose showed characteristic peaks at approximately 1653.66 cm^{-1} (1648-1658 cm^{-1} C=C stretching alkene), 1749.12 cm^{-1} (1735-1750 cm^{-1} C=O stretching δ-lactone), 1980.54 cm^{-1} (2000-1900 cm^{-1} C=C=C stretching allene medium), 2872.45 cm^{-1} (3000-2840 cm^{-1} C-H stretching alkane), 2974.66 cm^{-1} (3200-2700 cm^{-1} O-H stretching alcohol weak, broad, intramolecular bonded), 3477.03 cm^{-1} (3550-3200 cm^{-1} O-H stretching alcohol strong, broad-intermolecular bonded). Whey protein isolate (WPI) showed characteristic peaks at approximately 1375.96 cm^{-1} (1390- 1310 cm^{-1} O-H bending), 1667.16 cm^{-1} (1685-1666 cm^{-1} strong C=O stretching, conjugated ketone), 2353.69 cm^{-1} (2349 cm^{-1} strong O=C=O stretching), 2972.73 cm^{-1} (3000-2800 cm^{-1} strong, broad N-H stretching). Physical mixture: 3485.7cm^{-1} (3550- 3200cm^{-1} O-H stretching strong, broad-alcohol), 2929.34cm^{-1}(3000-2800 cm^{-1} amine salts N-H stretching strong, broad), 1978.61 cm^{-1}(2000-1900 cm^{-1} C=C=C stretching medium allene), 1747.19 cm^{-1} (1745 cm^{-1} C=O stretching cyclopentanone strong). 1649.8cm^{-1} (1650 cm^{-1} C=O stretching δ-lactam strong, 1421.28 cm^{-1} (1420-1330 cm^{-1} O-H bending alcohol medium)[12].

The % Encapsulation efficiency of PZQ-NSGs varied from 75.30±1.92 % to 93.26±2.21 % and drug loading was varied from 32.74±1.167% to 62.17±1.963%. Encapsulation efficiency increased with increasing concentration of cross-linker but in higher EC concentration batches it was found to be decreased. Highest drugencapsulation was found with batch F6. In order to support the increased solubility of the PZQ and PZQ-NSGs H-NMR investigations were performed. Mutually negative as well as positive minute proton shifts specified the occurrence of relations in formulated NSGs/complexes. Moreover, chemical shifts (δ 6-7) were observed for C-H (aromatic) for PZQ. As it obvious, the lowest shifts were observed for PZQ-NSGs complex indicated weak interactions with almost certainly negligible effect on PZQ properties. However polarizable (O-H, N-H, and N-CH) indicates the dipole-dipole interactions i.e. weak interaction was possibly seen between polymer-drug complex which leads to the conclusion that the sharp and intense peaks of drug got disappeared in formulation. The stability study was implemented for optimized freeze dried PZQ-NSGs as per ICH guidelines, shown Table IB. 34. Periodically samples were removed and checked for 1) physical appearance, entrapment efficiency, particle size and *in-vitro* drug release 2) Solid state characterization. PZQ-NSGs filled capsule does not showed any significant change in above parameters indicating stability of PZQ-NSGs for a period of 6 months[13].

The *in-vitro* drug release profile of the optimized freeze dried PZQ-NSGs (F6) formulation is depicted in Fig IB 79-81. It was observed that, formulation (F6) showed analogous to that of initial cumulative drug release profile which was done before stability. Thus, no significant difference has been revealed in the formulation when exposed at different temperature and humidity conditions like 25ºC ± 2ºC and RH 60% ± 5%, 30ºC ± 2ºC and RH 65% ± 5% and 40ºC ± 2ºC and RH 75% ± 5% as per the stability guidelines. The

% CDR study indicated that there was no significant difference observed as compared to the initial cumulative drug release profile of optimized freeze dried PZQ-NSGs.

The developed nanosponge drug delivery system were subjected to stability testing at higher temperature and humidity condition i.e. at 40ºC ± 2ºC and RH 75% ± 5 % after 6 months as per ICH guidelines. Solid state characterization of freeze dried PZQ-NSGs have been done with FTIR, PXRD, and particle size analysis. From above characterization it was observed that, the sample was remained stable at 40ºC ± 2ºC and RH 75% ± 5 % even after 6 months.

Conclusion

- The UV-visible spectrophotometric (UV) analytical method for the determination of PZQ was developed and validated for assay and stability study.
- There was no interference of different components observed with respect to time. The method was successfully validated as per ICH guidelines. A separate UV method for determination of PZQ was developed and validated for method specificity, linearity, accuracy, limit of detection and limit of quantification. UV spectroscopy method was developed for the investigation of dissolution samples[14].
- A series of such standard curves were constructed and the linearity range was determined in dist. water and different dissolution media (pH 1.2, 6.8 and 7.4).
- Suitable Polymer: and cross-linker ratio was selected to be the best for PZQ as per the result obtained at preliminary stage of formulation which exhibited lowest particle size, increased PZQ solubility and imparted desired stability to formulated PZQ-NSGs.
- The optimized batch of NSGs which was formulated by using emulsion diffusion method and which was in depth characterized at three key stages viz. nanosuspension (formulation) stage, freeze dried powder stage and capsule stage. Resulting nanosponges (Z- avg – 132 with 0.074 PDI) exhibited, pH dependent solubility (~13 folds seen in pH 6.8), rapid and pH dependant dissolution (>50% in 50minutes) in media (pH 6.8) dissolution studies. Significant enhancement in *in-vitro* dissolution traits in dissolution media pH 6.8 and biorelevant media was observed in comparison with plain drug and marketed formulation.
- Formulated nanosponges formulation was found to be stable at accelerated stability conditions as per ICH guidelines up to 6 months. Nanosized distribution, amorphous nature, better encapsulation and inclusion complexation with EC were found to be the major drivers for significant improvement in solubility, nanosized particles, dissolution efficiency and stability.

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