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Original Article

DEVELOPMENT AND EVALUATION OF NANOSPHERES CONTAINING CARBIMAZOLE

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ABSTRACT

Objective: To develop and evaluate polymeric nanospheres of Carbimazole using Nano-precipitation method.

Methods: The polymeric nanospheres of Carbimazole were prepared employing the nano-precipitation method using a varied concentration of Chitosan (polymer). The prepared formulations were characterized for several parameters such as SEM, Particle size, Micromeritic properties, Encapsulation efficiency, Degree of swelling, Percentage moisture loss, drug content, and *in vitro* drug release and release kinetics.

Results: Carbimazole-loaded polymeric nanospheres were developed, and the evaluation parameters depicted results within an acceptable range. The result of FTIR studies shows that there is no interaction between drug and excipients. The melting point, obtained as per the reference standard (122-125 °C) depicted the purity and authenticity of the drug. The micromeritics studies also supported the characterization of drug and excipients. The drug content was found to be in the range of 80.3±0.65 to 99.5±0.81 for all six formulations. The entrapment efficacy was obtained for all six formulations and ranged from 82.17 to 99.56. The release parameters were also observed for all formulations, and they were determined in the range of 82.5±0.4 for formulation NS6 (12 h) to 98.6±0.9 for formulation NS4 (24 h).

Conclusion: The results revealed thatthe formulation containing a higher concentration of Chitosan and a lower concentration of Tween 80 showed prolonged *in vitro* drug release in a controlled manner. Hence, On the basis of all formulation results, the NS4 was the best formulation among all.

Keywords: Carbimazole, Targeted drug delivery, Polymeric nanospheres, Chitosan, Nano-precipitation method

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INTRODUCTION

Nanospheres are colloidal particles of 10–200 nm that are spherical, polymer matrix-type nanoranged devices that consist of drug molecules present in dispersed phase in the polymer matrix [1]. Nanospheres are amorphous or crystalline in nature, and the drug molecules are dispersed in a solid skeleton formed by a polymer matrix. The Nanospheres are devised in order to tailor (control or sustain) the drug release, reduce the dosing frequency, and deliver the drug at the targeted or affected site [2]. Nanospheres have great potential for protecting drugs. The nanospheres are prepared by using either biodegradable (albumin, modified starch, gelatin) or non-biodegradable polymers (polylactic acid), and hence they are classified as Biodegradable nanospheres or non-biodegradable nanospheres [3].

Nanotechnology is the blend of science, engineering, and technology used in the production of nanoscale material. In pharmaceutical industries, the nanotechnological approach is used for its nano-range, controlled or sustained release drug delivery, improved therapeutic efficacy, improved bioavailability, drug delivery at targeted or affected sites, accurate dose with lesser or no adverse/side effects at other sites of the body, restrain hypersensitivity reaction, improved solubility of lipophilic drugs, improved stability and higher drug permeability [4, 5]. Now day's nanotechnology is the foremost approach used in the pharmaceutical industry since the beginning of the 21st century for its several advantages. The nano approach has been used in the formulation of medications for different routes of administration and treatment of many acute and chronic diseases. Nanotechnology has numerous platforms that include liposomes, polymeric nanoparticles (nanocapsules and nanospheres), nanosponges, nanoparticles, dendrimers, micelles, and nanoconjugates [6, 7].

Carbimazole is a prodrug of methimazole used in the treatment of hyperthyroidism and Grave's disease. It gets converted to its active form methimazole immediately after absorption and distributes and shows a therapeutic effect. This leads to frequent dosing of drugs which becomes very difficult for patients and reduces patient compliance. Hence, a novel drug delivery system is necessary for the fulfillment of the objectives raised. In this study, the polymeric nanospheres of Carbimazole are prepared by using varied concentrations of polymer (chitosan) employing the nano-precipitation technique.

MATERIALS AND METHODS

Carbimazole was obtained from Global calcium Pvt. Ltd. Hosur, Tamil Nadu Polymers and other excipients like, Chitosan, Tween 80 and other chemicals were of analytical grade obtained from college laboratory.

Methods

Polymeric nanospheres were prepared using the nanoprecipitation method. Table 1 shows the composition of each formulation. The nanospheres were prepared by dissolving a given quantity of polymer in water. Similarly, the drug was dissolved in methanol. Then, both of these solutions were mixed together at 10000 rpm for 5 min (min). Gleichzeitig, the aqueous solution of surfactant was added and stirred continuously. Thereafter, the solvent and water were evaporated using a rotary evaporator until a limited quantity of solvent remained. The mixture was then centrifuged at 15000 rpm at 4 °C for 30 min (min). The supernatant liquid was discarded, and the remaining portion was washed with distilled water. The obtained nanospheres were then dried and stored in desiccators for further characterization [8].

Table 1: Composition of polymeric nanospheres

S. No.	Ingredients	NS1	NS2	NS3	NS4	NS5	NS6
1	Drug (mg)	40	40	40	40	40	40
2	Chitosan (mg)	1	3	5	5	3	1
3	Methanol (ml)	10	10	10	10	10	10
4	Tween 80 (w/v) %	5	3	1	5	1	3
5	Water (ml)	10	10	10	10	10	10

Physiochemical characterization of carbimazole nanospheres

Particle size analysis

The particle size of batches was determined employing an optical microscope in which a thin layer of formulation was spread onto slide and observed [9].

Micromeritic properties

The nanospheres were characterized on micromeritic properties to determine the flow properties that include angle of repose, Bulk density, tapped density, Carr's index and Hausner's ratio.

Percentage moisture loss

The polymeric nanospheres were weighed (W_1) when formulated and then kept in desiccator containing $CaCl_2$ at 37 °C for one day(s). The final weight (W_2) was noted [10]. Percentage moisture loss was calculated using the formula:

$$\text{Percentage moisture loss} = \left[\frac{W1 - W2}{W2}\right] \times 100$$

Degree of swelling

The swelling ability of polymeric nanospheres was measured using physiological media (PBS pH 7.4). The polymeric nanospheres were weighed (W_o) when formulated and kept in buffer solution to allow it to swell for one day. The final weight (W_s) was measured [11]. The degree of swelling (α) of polymeric nanospheres was calculated using the formula:

$$\alpha = \frac{(Ws - Wo)}{Wo}$$

Encapsulation efficiency

The Encapsulation efficiency of polymeric nanospheres was calculated using the formula:

$$\text{Encapsulation Efficiency} = \frac{\text{Estimated \% Drug content}}{\text{Theoretical \% Drug content}} \text{ X } 100$$

Drug content

The (100 mg) batches of polymeric nanospheres were ground, weighed and placed in volumetric flask (100 ml). The flask was shaken and the flask was filled with PBS pH 7.4 up to the mark. The solution was further diluted to obtain 10µg/ml and the absorbance of the resulting diluted solution was analyzed for the drug content using UV spectroscopy at 290 nm [12].

Surface morphology

The SEM was carried out to determine the shape and surface morphology of batches and photograph was taken for the same.

***In vitro* drug release studies**

The releaserate of prepared batches was determined employing USP dissolution testing apparatus II. The dissolution testing was performed using 900 ml of phosphate buffer Ph 7.4 at 37±0.5 °C temperature and paddle speed 50 rpm. Sample of 5 ml was withdrawn at 2 min interval of time up to 20 min and replaced with fresh medium to maintain sink condition and the percentage of drug release was determined using UV spectrophotometer at 295 nm [13].

RESULTS AND DISCUSSION

Surface morphology

The SEM was carried out to determine the shape and surface morphology of batch (NS3). The photographs of polymeric nanospheres are shown in fig. 1.

The particle size of batches was found to be between 168±0.3 to 196.7±0.58 (table 2) Other micromeritic properties such as bulk (0.534±0.05 of NS1 to 0.592±0.1 NS3) and tapped density (0.612±0.018 NS1 to 0.675±0.014 NS3), Carr's index (9.6±0.2 NS2 to 14.06±0.3 NS6), and Hausner's ratio (1.10±0.18 NS2 to 1.17±0.3 NS6) The nanospheres (NS1-NS6) showed good flow properties as determined from the results of angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio (table 2).

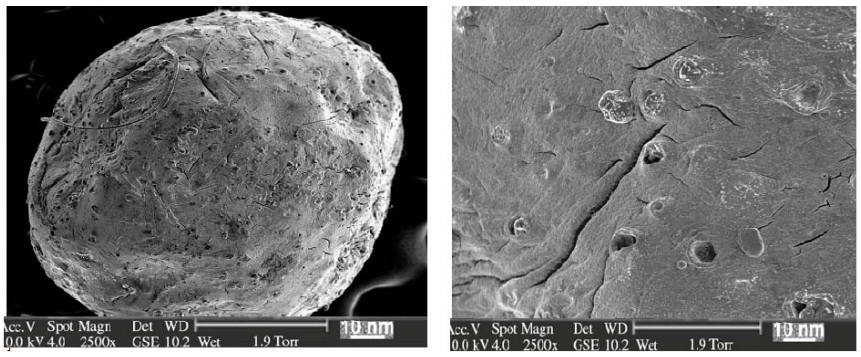

Fig. 1: SEM results of carbimazole nanoparticles

Table 2: Micromeritic properties of polymeric nanospheres (NS1-NS6)

Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
NS1	24.5±0.58	0.534±0.05	0.612±0.018	13.11±0.4	1.14±0.29
NS2	26.8±0.61	0.568±0.069	0.621±0.022	9.6±0.2	1.10±0.18
NS3	28.7±0.88	0.592±0.1	0.675±0.014	11.94±0.6	1.13±0.2
NS4	25.8±0.57	0.588±0.07	0.664±0.017	12.12±0.5	1.13±0.25
NS5	27.4±0.21	0.574±0.06	0.668±0.089	13.63±0.6	1.15±0.1
NS6	29.2±0.65	0.554±0.02	0.649±0.018	14.06±0.3	1.17±0.3

All data showed as means (n=3); where n is the number of observations

Table 3 and fig. 2 have shown the % moisture loss was minimal in the range 5.3±0.2 NS1 to 6.2±0.2 NS6. Other parameters like degree of swelling range from 84.2±0.21 (NS1) to 98.1±0.67 (NS4), encapsulation efficiency from 82.17±0.38 (NS6) to 99.56±0.31 (NS4), and drug content from 80.3±0.65 (NS1) to 99.5±0.81(NS4).

Table 3: Characterization of polymeric nanospheres (NS1-NS6)

Formulation	% moisture loss	Degree of swelling	Drug entrapment efficiency (%)	Drug content
NS1	5.3±0.2	84.2±0.21	84.62±0.25	80.3±0.65
NS2	5.6±0.1	89.4±0.36	91.35±0.51	89.5±0.54
NS3	5.5±0.5	97.2±0.54	94.5±0.45	92.6±0.48
NS4	5.5±0.2	98.1±0.67	99.56±0.31	99.5±0.81
NS5	5.9±0.3	94.6±0.51	96.4±0.64	95.2±0.67
NS6	6.2±0.2	85.4±0.81	82.17±0.38	80.6±0.88

All data showed as mean±SD (n=3); where n is the number of observations

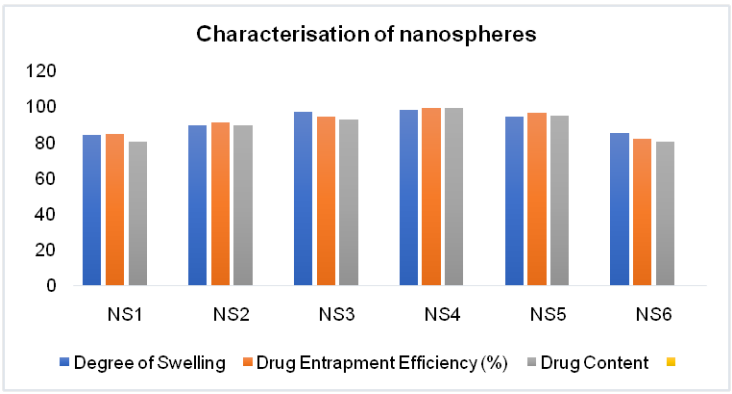

Fig. 2: Characterization of nanospheres

The release rate of drug loaded nanospheres was determined. The release of drug from nanospheres was noted at regular time intervals the formulation NS4 exhibited the release 4.35±0.1 % in one hour, which is the lowest among all the formulation while formulation NS1 11.8±0.6 %, highest release. After 6 h, formulation NS6 released 80.5±0.8, whereas NS2 released 54.2±0.3 % drug. In the time interval of 12 h, the formulation NS5demonstrated 82.5±0.1 % drug release and NS4 88.6±0.9%. After 12 h study it was observed that no further changes in drug release was observed in formulation NS1 and NS 6 while the maximum release of drug was observed in formulation NS4. Drug *in vitro* release data are shown in table 4 and the graphical representation is shown in fig. 3.

Table 4: % cumulative drug release

Time (h)	% cumulative drug release					
	NS1	NS2	NS3	NS4	NS5	NS6
1	11.8±0.6	7.4±0.1	5.6±0.7	4.35±0.1	8.5±0.1	12.4±0.9
2	28.5±0.4	14.5±0.5	13.5±0.1	12.5±0.5	15.6±0.3	29.5±0.1
3	42.6±0.5	23.6±0.2	18.4±0.1	17.7±0.5	24.3±0.5	41.2±0.5
4	59.8±0.04	29.2±0.7	28.2±0.5	30.6±0.3	30.6±0.7	60.8±0.4
5	74.3±0.5	41.3±0.1	39.6±0.8	38.4±0.5	42.5±0.9	75.4±0.9
6	80.8±0.3	54.2±0.3	55.7±0.08	56.6±0.4	54.22±0.5	80.5±0.8
12	84.9±0.2	84.5±0.5	85.28±0.1	88.6±0.9	82.6±0.1	82.5±0.4
24	-	90.5±0.5	93.28±0.1	98.6±0.9	95.6±0.1	-

All data showed as mean±SD (n=3); where n is the number of observations

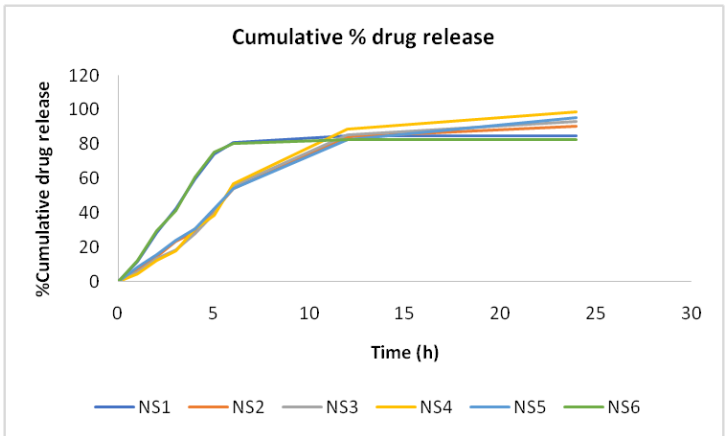

Fig. 3: % Cumulative drug release for polymeric nanospheres (NS1-NS6)

DISCUSSION

The Micromeritics properties like angle of repose, was determined and it was found in the range of 24.5 to 29.2. It was indicating that nanospheres have good flow properties [14]. The other micromeritics properties like bulk density0.534±0.05 of NS1 to 0.592±0.1 NS3), tapped density (0.612±0.018 NS1 to 0.675±0.014 NS3), carr'sindex (9.6±0.2 NS2 to 14.06±0.3 NS6), and Hausners's ratio (1.10±0.18 NS2 to 1.17±0.3 NS6). When data were compared with refence article Ghosal K *et al.* (2022), parameters were found in the limits and exhibits the good compressibility of nanospheres [15].

Swelling property of nanospheres important parameters of for indicating the dissuasion of drug. It has observed that while increasing the concentration of polymers (Chitosan) in the formulation (NS4, 5%), the swelling property of nanospheres is also increased as suggested by Sharma R *et al.*, (2012). The swelling aspects of nanospheres reflecting a gel like structure around the nanospheres, controlled the drug release of drug [16].

Drug entrapment efficiency of drug is another crucial aspect of nanospheres. It has observed that formulation NS4 (5%) shown the best drug entrapment efficiency among all six formulations because of higher concentration of polymer and surfactant Tween 80 (5%), due to its lipophilic nature.

Drug Content also an important aspect of any dosage form for its therapeutic action. The Formulation NS4 possess most drug content in its vesicle (99.5±0.81). The dissolution studies are the very important aspects of any dosage form and it reflects the dissolution studies. The Formulation NS4 has shown promising results in terms of drug release, drug entrapment efficiency, swelling, drug content, and R^2(99.26) value. The high concentration of polymer chitosan (5%) and surfactant Tween 80 in Formulation NS4 seems to have contributed to the desirable drug release profile, with approximately 99% drug release achieved within 24 h. The results when compared with reference research articles Sharma R *et al. (*2022). The results are supported with reference standard [17].

The controlled and sustained drug release observed in Formulation NS4 is a desirable characteristic in nanosphere-based drug delivery systems. The high drug entrapment efficiency indicates that a significant amount of the drug is effectively encapsulated within the nanospheres, ensuring efficient drug delivery to the target site. Additionally, the proper swelling behavior can contribute to the controlled release of the drug from the nanospheres.

Furthermore, the high drug content in Formulation NS4 ensures that a consistent amount of drug is present in each nanosphere, which is crucial for achieving consistent therapeutic effects. The R^2 value, which is a measure of how well the drug release data fits the chosen release model, likely indicates that the drug release from Formulation NS4 follows a well-defined pattern.

The mathematical models were used to evaluate the kinetics and mechanism of drug release. The model that gave high correlation coefficient (r) value was considered as the best fit of the release data. Data of *in vitro* release were fitted to different Equation and kinetic models to explain the release kinetics of drug from the nanospheres. The data were processed for regression analysis using MS-Excel statistical functions. To know the order of reaction from these formulations, the data were treated according to first-order (log cumulative percent drug remaining vs. time), Higuchi's (cumulative percent drug released vs. square root of time), and Korsmeyer Pappas's (log cumulative percent drug released vs. log time) Equations along with zero order (cumulative amount of drug released vs. time) Equation. From the release kinetics of nanospheres table 4, it was found that the zero-order release kinetics was best fitted. As per Jain A. *et al.*, 2016, the controlled drug delivery system is best suited for zero order kinetics since it releases the drug at constant pace for longer duration [18]. The correlation coefficient (R^2) was used as an indicator of the best fitting and was found to be highest for zero order model kinetic. The mechanisms of drug release are non-Fickian diffusion (anomalous transport) with "n" value less than 1. This indicates the drug release depends on swelling and diffusion mechanism of release.

The prepared and optimized nanospheres (NS4) was packed and subjected to stability studies at 45±2 °C and 75±5 °C relative humidity for 90 d. Samples were withdrawn at time zero and after 15, 30, 60, and 90 d and evaluated for organoleptic properties (color, odor, and appearance), drug entrapment efficiency and dissolution. It was observed that there was no significant change all parameters during the study [19].

CONCLUSION

It was concluded that among all the batches, Carbimazolenanospheres prepared using higher concentration of Chitosan and lower concentration of Tween 80 showed significantly prolonged drug release. The results proved the ability of the nanospheres to monitor the drug release, reduce dosing frequency and improve patient compliance. Carbimazole nanospheres can be a successful approach in treatment of hyperthyroidism and Grave's disease. The nanosphere formulation of carbimazole drug faces limitations in terms of potential stability issues during storage, challenges in achieving uniform particle size distribution, and potential complexities in the scale-up of production processes.

ABBRIVATIONS

r2-Correlation coefficient, USP-United States Pharmacopoeia, PBS-Phosphate Buffer Solution, EE-Entrapment efficiency, SEM-Scanning Electron Microscopy, rpm-Revolutions per minute, mg-Milligram, nm-Nanometer, g/ml-Gram per milliliter.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest regarding the publication of the paper.

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