ORIGINAL ARTICLE

Formulation and evaluation of hydroxyzine hydrochloride sustained release microspheres by ionotropic gelation technique using Carbopol 934P

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Preparation of sustained release microspheres of hydroxyzine hydrochloride by ionotropic gelation technique and evaluation. Microspheres of hydroxyzine hydrochloride were prepared by ionotropic gelation method using sodium alginate, Carbopol 934P and calcium chloride. The powders were evaluated for their flow properties. Hydroxyzine hydrochloride microspheres were characterized by Fourier transform infrared and *in vitro* dissolution studies. The drug release study of hydroxyzine hydrochloride microspheres was evaluated using basket type dissolution test apparatus. The release rate of Hydroxyzine hydrochloride microspheres was studied for 12 h in pH 7.4 phosphate buffer media. From the five batches F5 batch showed good release behavior 91.08% of drug is released over 12 h, and $r^2 = 0.987$ in zero-order kinetics. The microspheres were prepared without the use of organic solvents. Microspheres of hydroxyzine hydrochloride decrease the incidence of side effects and also improve patient compliance by reducing the number of dosing and by reducing the fluctuations of drug in the blood. This entire attributed attitude proves that microsphere technology from novel drug delivery can be very much effective in reducing dosage frequency, dose dumping, and better patient compliance and economical to the patient. In the future, natural, biodegradable polymers can be used to improve therapeutic efficacy of the drug and further minimizing side-effects.

Key words: *Carbopol 934P, hydroxyzine hydrochloride, ionotropic gelation technique, microspheres, sodium alginate*

INTRODUCTION

Hydroxyzine is a first-generation antihistamine of the diphenylmethane and piperazine classes. It was first synthesized by Union Chimique Belge in 1956.[1] Due to its antagonistic effects on several receptor systems in the brain, hydroxyzine has strong anxiolytic and mild antiobsessive as well as antipsychotic properties.[2,3] Because of its antihistamine effects it can also be used for the treatment of severe cases of itching, hyperalgesia and motion sickness-induced nausea. The conventional dosage form are available in the market, but it requires frequent dosing, To overcome the limitations of conventional therapy, sustained/controlled release dosage forms are designed which are able to maintain steady state drug plasma levels for extended periods of time as a result of which the variations of the drug levels in the blood and drug-related side effects are minimized.[1] Sustained release preparations are useful to reduce the dosage frequency to improve patient convenience, In order to reduce the gastrointestinal adverse effects of this drug, several swellable controlled-release pharmaceutical dosage forms have been developed.[4] From literature survey, it is evident that multiple unit systems are better distributed and tend to cause lesser gastrointestinal tract irritation. The sustained release formulations proved to

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Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.143934

minimize the side effects.[3] Furthermore, administration of antihistaminic drug incorporated multiparticulates can avoid the undesired intestinal retention of polymeric material, which can occur in case of a single unit form, particularly on chronic dosing.[5] When orally administering hydroxyzine hydrochloride conventional formulation, it was difficult to achieve the desired clinical effect and moreover dose dumping also increases.

In recent times, many new approaches are developed to attain the peak plasma concentration and to minimize the frequency of dosing. Microsphere is also a great achievement to attain the sustained release. Moreover, sodium alginate used in the preparation are water soluble, and they are salt form of alginic acid is a linear copolymer with homopolymeric blocks of (1-4)-linked β-D-mannuronate (M) and its C-5 epimer α-L-glucuronate (G) residues, respectively covalently linked together in different sequences or blocks. The monomers can appear in homopolymeric blocks of consecutive G-residues (G-blocks), consecutive M-residues (M-blocks) or alternating M and G-residues.[6]

Microspheres are characteristically free flowing powders consisting of protein or synthetic polymers which are biodegradable in nature and ideally having particle size 200–800 μm.[7-9] Microparticles play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects.[10]

The rationale of developing sustained release.

- To extend the duration of action of the drug
- To reduce the frequency of dosing
- To minimize the fluctuations in plasma level
- Improved drug utilization
- Less adverse effects.

The objective of the present study was to develop microspheres of hydroxyzine hydrochloride by ionotropic gelation technique using hydrophilic carrier Carbopol 934P to sustain the release so as to reduce the frequency of dosing and to improve patient compliance.[1-3]

MATERIALS AND METHODS

Hydroxyzine hydrochloride was obtained as gift sample from Pulson Drug Pharmaceuticals Pvt. Ltd. (Derma Division). Carbopol 934P, sodium alginate, calcium chloride were obtained as gift sample from Merk Laboratories. Potassium dihydrogen phosphate was obtained as gift sample from RFCL Limited. All other chemicals/reagents used were of analytical grade.

In ionotropic gelation technique, the preparation of drug containing microparticles is based on the principle of coalescence of colloidal polymer particles. Ionotropic gelation of the anionic polysaccharide sodium alginate with oppositely charged calcium ions forms microparticles. Subsequent curing step induces the fusion of colloidal polymer particles into a homogenous matrix. During the coating and drying process, the colloidal polymer particles coalesce and fuse into a homogenous film.[11] It is a cost effective technique that establishes intimate contact of the drug with the release retardant.

Alginate is a natural biopolymer which has been used widely due to its nontoxic, biodegradable and biocompatible nature. Alginic acid is a linear copolymer of p-o-mannuronic acid and u-L-guluronic acid linked by (1-4)-glycosidic bonds.[12] Alginate gelation takes place when divalent cations, interact ionically with blocks of guluronic acid residues, resulting in the formation of a three-dimensional network.[13] Sodium alginate is soluble in water and forms a reticulated structure which is cross-linked with divalent calcium chloride to form insoluble meshwork. Alginate's unique property of forming water insoluble calcium alginate gel through ionotropic gelation with calcium ions is a simple, mild and eco-friendly condition to encapsulate drugs. Another important property of alginate beads is their re-swelling ability. This property is sensitive to the environment pH. Alginate has a property of coating on the drug core and also acts as release rate retardant.[14]

Method

Method of preparation of microsphere by ionotropic gelation technique

Microspheres of hydroxyzine hydrochloride were prepared by ionotropic gelation method using sodium alginate, Carbopol 934P and calcium chloride. Weighed quantity of drug and polymer were added to 50 ml of sodium alginate solution with stirring at about 300 rpm. The resultant solution was then added drop wise to 100 ml of calcium chloride solution under continuous stirring. Stirring was continued for 30 min. The obtained microspheres were filtered and washed with purified water and then dried for 6 h at 40°C. Preparation of microspheres was optimized based on entrapment efficiency and release data. The dried microspheres were sifted through mesh 30 ASTM. Batch wise distribution of the ingredients shown in Table 1.

Particle size analysis

The particle size of the microsphere was determine using optical microscopy method; approximately 100 microsphere were counted for particle size using a calibrated optical microscope,[15,4] which is shown in Table 2 and Figure 1.

Micromeritic properties

Micromeritic properties hydroxyzine hydrochloride microspheres shown in Table 3.

Angle of repose

Angle of repose was determined by using funnel method. The granules were poured from funnel that can be raised vertically until a maximum cone height '*h*' was obtained. Then

Table 1: Batch wise distribution of the ingredients

Formulation code	Drug: Carbopol 934P	Sodium alginate solution (% w/v)	Calcium chloride solution (% w/v)
F1	1:5	4	5
F2	1:4	4	5
F3	1:3	4	5
F4	1:2	4	5
F5	1:1	4	5

Table 2: Determination of average particle size, percentage of drug loading and percentage of entrapment efficiency

Batch code	Average particle size (μm)	Percentage of drug loading	Percentage of entrapment efficiency
F1	44.16±3.03	2.09±0.035	12.8±0.658
F2	45.02±1.62	3.72±0.065	46.47±2.48
F3	47.07±2.32	4.59±0.026	80.12±2.19
F4	50.47±1.15	2.20±0.02	14.56±0.248
F5	49.23±1.87	4.19±0.04	53.53±1.18

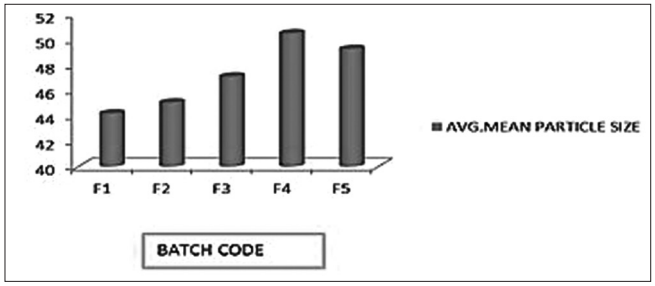

Figure 1: Average mean particle size

the diameter of the powder cone was measured, and the angle of repose was calculated using the following equation. $\theta = \tan - 1\ (h/r)$.[19]

Bulk density and tapped density

Bulk density of powder blend for hydroxyzine hydrochloride

Apparent bulk density was determined by placing presieved granules into a graduated cylinder and measuring the volume and weight as it is.[20,21] The bulk density was calculated by using following formula. Bulk density = Weight of powder/ volume of packing.

Tapped density

A quantity of 2 g of powder from each formula was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allow to fall under its own weight on the hard surface from the height of 2.5 cm at 2 s intervals. The tapping was continued until no further change in the volume was noted.[16-18] The tapped density was calculated by using following formula. Tapped density = Weight of powder/ tapped volume of packing.

Compressibility index of powder blend for hydroxyzine hydrochloride

Compressibility index of granules was determined by Carr's compressibility index. Carr's index: ([Tapped bulk density (TBD) - loose bulk density (LBD)] ×100)/TBD.

Hausner ratio of powder blends for hydroxyzine hydrochloride

Hausner ratio was determined by using the ρ_T is LBD and ρ_T is TBD.

Hausner ratio is <1.25 is considered to be an indication of poor flow ability. Hausner ratio = ρ_T/ρ_B.

Determination of maximum wavelength of hydroxyzine hydrochloride in phosphate buffer (pH 7.4)

Hydroxyzine hydrochloride was accurately weighed and dissolved in 10 mmol phosphate buffer of pH 7.4 to prepare a stock solution of 1 mg/ml. The stock solution was further diluted to 10 mcg/ml with diluent (10 mmol phosphate buffer of pH 7.4) then the diluted solution was scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu UV/visible spectrophotometer Model UV – 1700, SHIMADZU CORPORATION. International Marketing Division, 3. Kanda-Nishikicho 1-chome, Chiyoda-ku, Tokyo 101-8448, Japan) in the range of 200-400 nm, using 10 mmol phosphate buffer of pH 7.4 as blank. The λmax was found to be 230.5 nm.

Drug – polymers interaction study

Differential scanning calorimetric of the hydroxyzine hydrochloride and excipients to study the interaction between components

The differential scanning calorimetric (DSC) study of hydroxyzine hydrochloride in formulation indicating that there was no interaction between the drug-excipients, which is shown in Figure 2.

Fourier transform infrared spectroscopy of the hydroxyzine hydrochloride and excipients to study the interaction between components

The Fourier transform infrared (FT-IR) spectrum of hydroxyzine hydrochloride in formulation indicating there was no interaction between the drug-excipients. They were scanned over a wave number range of 4000 cm^{-1}-400 cm^{-1} using FT-IR (Perin Elmer, USA, Model: Spectrum one, Version A) is shown in Figure 3.

***In vitro* dissolution studies**

The *in vitro* studies were carried out in 900 ml of phosphate buffer, pH 7.4, maintained in 37°C ± 0.5°C and 75 rpm by using united states pharmacopoeia basket type dissolution test apparatus (Testing Instruments, Kolkata) under sink conditions, Take 100 mg equivalent drug's microspheres were added to dissolution medium and at present time intervals, 5 ml aliquots were withdrawn and replaced with an equal volume of fresh dissolution medium. After suitable

Table 3: Micromeritic properties hydroxyzine hydrochloride microspheres

Formulation code	Angle of repose (θ)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner ratio
F1	14.52±0.25	0.715±0.005	0.772±0.020	7.383±0.075	1.079±0.010
F2	15.42±0.32	0.720±0.008	0.784±0.008	8.163±0.008	1.088±0.007
F3	15.25±0.43	0.705±0.015	0.751±0.018	6.125±0.016	1.0652±0.046
F4	12.29±0.28	0.688±0.021	0.754±0.006	8.753±0.12	1.095±0.003
F5	13.42±0.35	0.709±0.002	0.762±0.017	6.955±0.018	1.074±0.027

Table 4: Zero order drug release rate

Time in hour	Cumulative percentage of drug release				
	F1	F2	F3	F4	F5
1	19.34	10.23	25.62	22.12	12.10
2	24.06	18.70	34.05	36.29	23.60
3	38.21	27.44	45.76	47.12	38.42
4	47.01	32.48	52.43	67.07	44.57
6	62.37	60.04	60.24	72.73	68.27
10	75.24	77.83	75.23	82.34	80.26
12	82.22	85.67	84.43	87.32	91.08

Table 5: First order drug release rate

Time in hours	Log cumulative percentage of drug release				
	F1	F2	F3	F4	F5
1	1.286	1.009	1.408	1.344	1.082
2	1.381	1.271	1.532	1.559	1.372
3	1.582	1.438	1.660	1.673	1.584
4	1.672	1.511	1.719	1.826	1.649
6	1.794	1.778	1.779	1.861	1.834
10	1.876	1.891	1.876	1.915	1.904
12	1.914	1.932	1.926	1.941	1.959

Table 6: Higuchi model of drug release rate

Square root of time in hours	Cumulative percentage of drug release				
	F1	F2	F3	F4	F5
1	19.34	10.23	25.62	22.12	12.10
1.414	24.06	18.70	34.05	36.29	23.60
1.732	38.21	27.44	45.76	47.12	38.42
2	47.01	32.48	52.43	67.07	44.57
2.449	62.37	60.04	60.24	72.73	68.27
3.162	75.24	77.83	75.23	82.34	80.26
3.464	82.22	85.67	84.43	87.32	91.08

Table 7: Koresmeyer–Peppas of drug release rate

Log of hour	Log cumulative percentage of drug release				
	F1	F2	F3	F4	F5
0	1.286	1.009	1.408	1.344	1.082
0.301	1.381	1.271	1.532	1.559	1.372
0.477	1.582	1.438	1.660	1.673	1.584
0.602	1.672	1.511	1.719	1.826	1.649
0.778	1.794	1.778	1.779	1.861	1.834
1	1.876	1.891	1.876	1.915	1.904
1.079	1.914	1.932	1.926	1.941	1.959

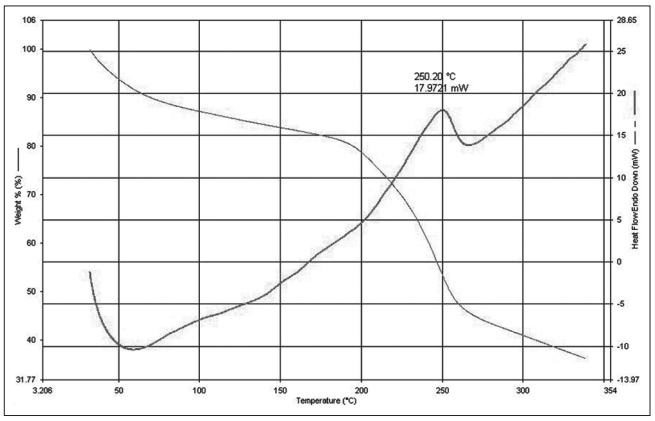

Figure 2: Differential scanning calorimetric result of hydroxyzine hydrochloride + Carbopol 934P

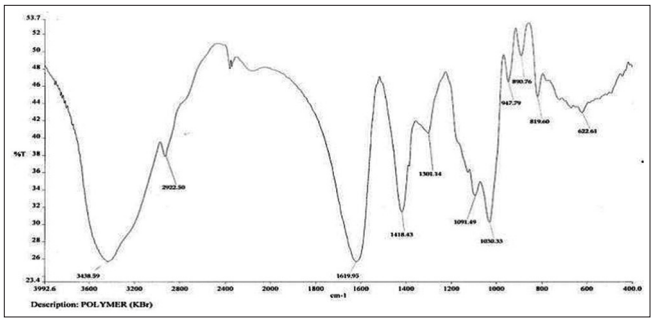

Figure 3: Fourier transform infrared of hydroxyzine hydrochloride + Carbopol 934P

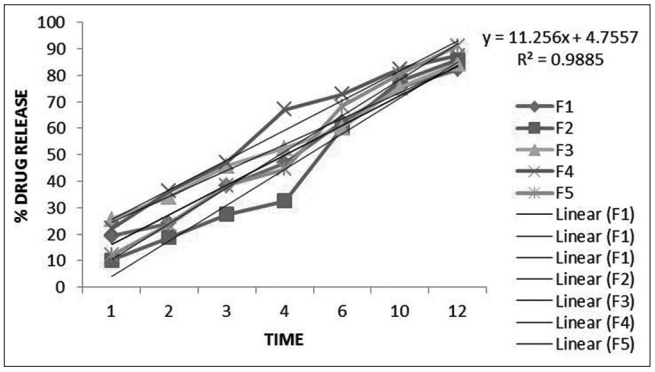

Figure 4: Zero order drug release rate

dilution, the samples were analyzed spectrophotometrically at 230.5 nm which is shown in Tables 4-7 and Figures 4-7. The

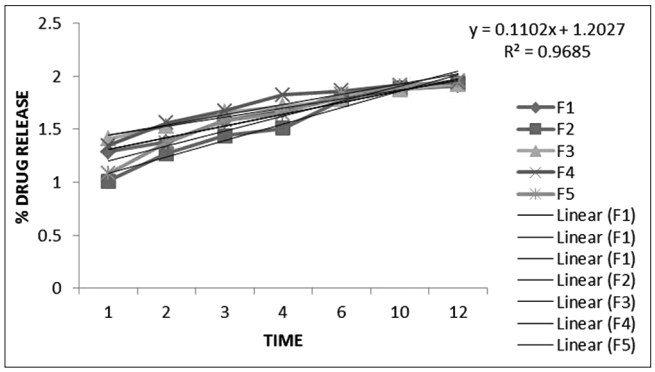

Figure 5: First order drug release rate

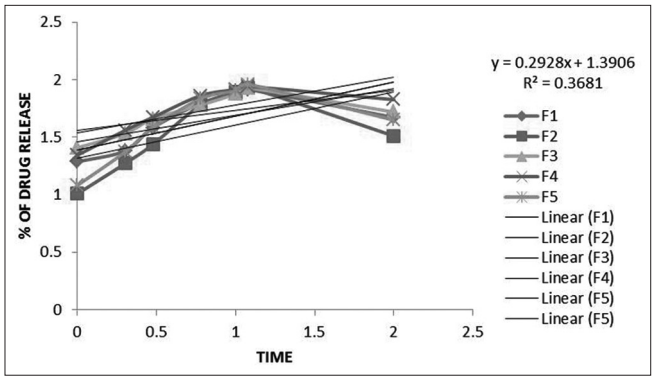

Figure 7: Koresmeyer–Peppas model for drug release

concentration of hydroxyzine hydrochloride in test samples was corrected and calculated by following formula:

([Test absorbance/standard absorbance] × [standard concentration/test concentration]) ×100.

Percentage yield

The prepared microspheres of all batches were accurately weighed. The measured weight of prepared microspheres was divided by total amount of all the excipients and drug used in the preparation of the microspheres, which give the total percentage yield of microspheres.[22]

Drug entrapment efficiency

Percentage of drug loading shown in Figure 8.

Encapsulation efficiency = (actual drug loading/theoretical drug loading) ×100%.

Release kinetics

To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted into, zero order, the first order, higuchi matrix, and Peppas model. The '*r*' values obtained were compared to judge the best fit model.[23]

Stability studies

The success of an effective formulation was evaluated only through the stability studies. The purpose of stability testing

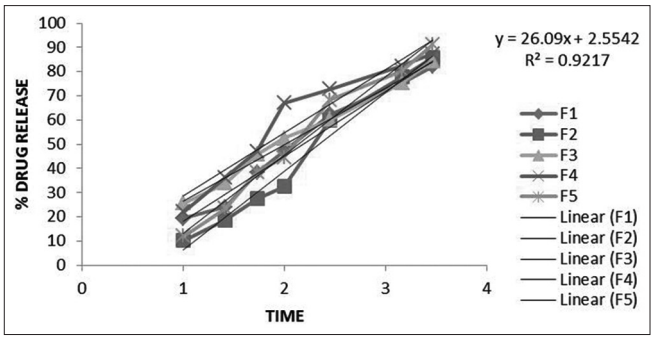

Figure 6: Higuchi model of drug release rate

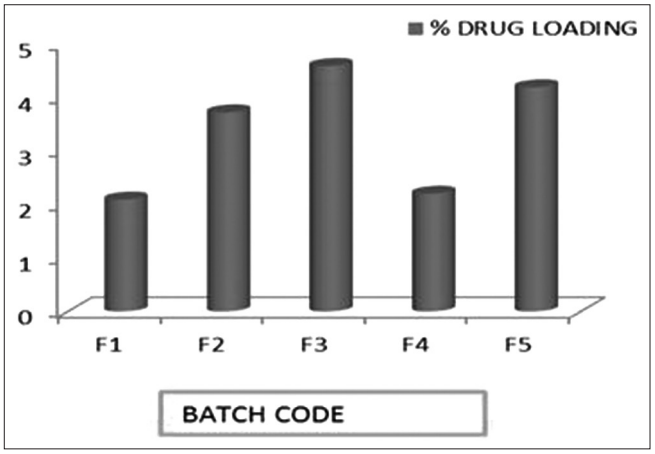

Figure 8: Percentage drug loading

was to obtain a stable product which assures its safety and efficacy up to the end of shelf life. In this study, stability study was done for at conditions like Room temperature, 30°C and 60% RH, 40°C and 75% RH. The samples were assayed for drug content at regular intervals for 2 weeks percentage of drug content of F5 during stability study shown in Table 8.

Statistical analysis

Data were analyzed for statistically significant differences by one-way analysis of variance. The level of significance was taken as $P < 0.05$.

RESULTS AND DISCUSSION

Study of micromeritic properties

The values of angle of repose of all type of formulations within the range from 12.29 ± 0.28 to 15.42 ± 0.32. All type of microspheres exhibits excellent free flow properties. Values of Carr's index and Hausner ratio also support the good flow properties as well as good compaction properties depicted in Table 3. Hence, that required dose quality can be dispensed through capsules bodies.

Drug entrapment and content uniformity studies

The analysis of drug content showed a maximum entrapment efficiency of 80.12% ±2.19% at the drug-polymer ratio

of 1:3. Overall, drug entrapments were found to range between 12.8% ±0.658% and 80.12% ±2.19%. It was found that percentage drug loading and percentage entrapment efficiency ware maximum in formulation F3 Table 2.

Fourier transform infrared studies

Fourier transform infrared spectra study showed no change in the fingerprint region of pure drug spectra. This confirms the absence of drug to polymer interaction Figure 3. FT-IR spectra revealed that there was no such interaction between the drug and the polymers used for microsphere formulation.

Scanning electron microscopy study

Scanning electron microscopy (SEM) study showed that the particles made of Carbopol 934P were spherical and free flowing. The SEM image of hydroxyzine hydrochloride-containing microspheres is shown in Figures 9 and 10. The microspheres were discrete, free-flowing and spherical. Presence of pores was detected on the surface, which increased in size and number with respect to time after dissolution, indicating leaching of the drug through these channels.

Differential scanning calorimetric study

The DSC study of Hydroxyzine hydrochloride in formulation indicating that there was no interaction between the drug and excipients, which is shown in Figure 2.

***In vitro* dissolution studies**

In vitro dissolution studies of all batches of microspheres were shown in Tables 4-7 and Figures 4-7. Microspheres made of Carbopol 934P showed good flow properties and maximum releasing tendency. The release of drug from microspheres was gradual without producing a dose dumping effect.

For the purpose of above research project, five batches of hydroxyzine hydrochloride were prepared in the form of microspheres (batch no - F1, F2, F3, F4, F5) using different grades and ratio variation of polymer mainly Carbopol 934P and sodium alginate. Out of the above batches, the batch no F5 showed good release behavior 91.08% of drug are released over 12 h and when the kinetics study of all batches were compared. All the batches followed mainly zero-order kinetics and batch no-F5 showed the $r^2 = 0.987$ in zero-order kinetics. Cumulative percentage of drug release was found above 80% in 12 h in all cases, but the uniform release had been followed in formulation F3. From the batch no - F1, F2, F4 also showed good release behavior over 12 h.

An SEM study of the batch F5 before and after dissolution also showed good release behavior shown in Figures 9 and 10.

Table 8: Percentage of drug content of F5 during stability study

Time in days	Percentage of drug content (in room temp and humidity)
0	72.77
30	74.62
60	74.49
90	75.06

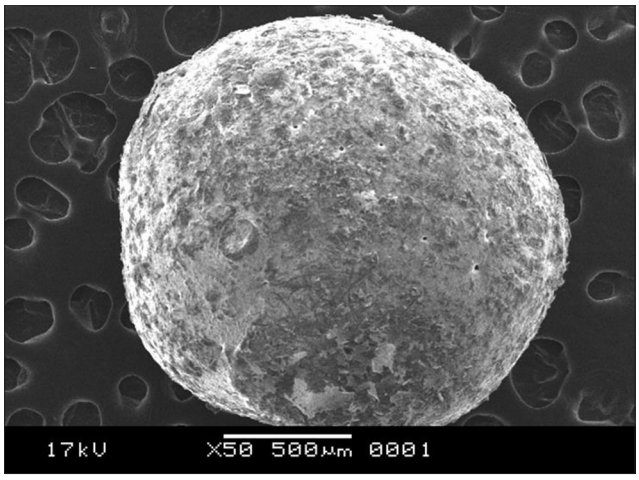

Figure 9: Scanning electron microscopy of microsphere before dissolution

CONCLUSION AND FUTURE SCOPE

Sustained release formulation of Hydroxyzine hydrochloride was successfully prepared using sodium alginate in combination with Carbopol 934P as a polymer by ionotropic gelation technique. The *in vitro* dissolution data showed sustained release of the formulation up to 12 h. The microspheres were prepared without the use of organic solvents. Microspheres of Hydroxyzine hydrochloride decrease the incidence of side effects and also improve patient compliance by reducing the number of dosing and by reducing the fluctuations of drug in the blood. Different ratio of polymer Carbopol 934P are taken along with drug Hydroxyzine hydrochloride and all the batches F1, F2, F3, F4, F5 good results in drug entrapment efficiency, drug loading, particle size and r^2 value in zero order, Higuchi model, Koresmeyer–Peppas model except first order. This entire attributed attitude proves that Microsphere technology from novel drug delivery can be very much effective in reducing dosage frequency, dose dumping, and better patient compliance and economical to the patient. In the future, natural, biodegradable polymers can be used to improve therapeutic efficacy of the drug and further minimizing side effects.

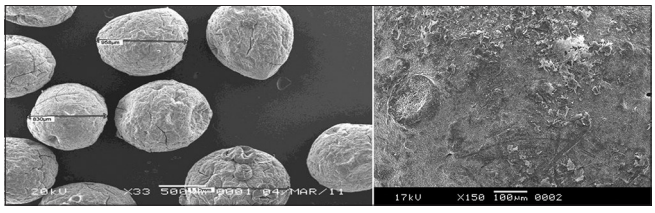

Figure 10: Scanning electron microscopy of microsphere after dissolution

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How to cite this article: Ghosh S, Majumder S, Pal R, Chakraborty M, Biswas A, Gupta BK. Formulation and evaluation of hydroxyzine hydrochloride sustained release microspheres by ionotropic gelation technique using Carbopol 934P. Asian J Pharm 2014;8:230-6.

Source of Support: Nil. **Conflict of Interest:** None declared.