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MINIMIZATION OF INITIAL BURST IN ALGINATE HYDROGEL BEADS BY IONOTROPIC GELATION METHOD

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ABSTRACT
The work investigates the minimization of initial burst in alginate hydrogel beads by ionotropic gelation method. The design of effective and safe drug delivery systems has become an integral part for the development and formulating of new medicines. So, research continuously keeps on searching for new ways to deliver drugs over a long period of time or for a well-controlled release profile, to minimizing the loss of drug, to reduce the side effect. The beads were prepared by using sodium alginate coated with chitosan, containing Metformin hydrochloride by ionotropic gelation using central composite design. The influence of various formulation factors such as *In-vitro* drug release, drug entrapment efficiency, swelling study, bead size and micromeritic properties, was investigated. These were also characterized by Scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR) analysis. Metformin hydrochloride containing hydrogel beads were in the size range of 1.84±0.02 to 2.00±0.15 mm. Metformin hydrochloride loading amount, concentration of chitosan, polymer concentration and cross-linking agent seemed to affect the values of particle size. It was found that the particle size decreased significantly by increasing sodium alginate concentration. The drug entrapment efficiency was found in the range of 86.14±1.85 to 93±1% and the drug release were found at 8 h in the range 70±0.49% to 90.84±0.94%. The release pattern observed was a biphasic, characterized by an initial burst effect followed by slow release. No significant change was found in the drug content of drug-loaded beads, stored at room temperature and 40°C after 60 days of study.

KEYWORD- Hydrogel beads, Metformin hydrochloride, Sodium alginate, chitosan, Ionotropic gelation technique, Optimization.

INTRODUCTION
Oral drug delivery is the most widely utilized routes for administration among all alternatives that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage forms. Popularity of the route may be ease of administration as well as traditional belief that by oral administration of the drug is due to the well absorbed into the food stuff ingested daily.[1] Sustained release (SR), Controlled release (CR) pharmaceutical products have gradually gained medical acceptance and popularity. Regulatory approval for marketing and their pharmaceutics superiority and clinical benefits over immediate release pharmaceutical products have been increasingly recognized.[2] Oral controlled release drug delivery is thus a drug delivery system that provides a continuous oral delivery of drug at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit.[3] There are several terms used interchangeably that is Controlled release, programmed release, sustained release, prolonged release, timed release, slow release, extended release.[4] The controlled release formulation overcome many of the drawbacks of conventional dosage forms Controlled release formulations are not associated alternating periods toxic level or sub therapeutic concentration, thereby improving the therapeutic efficacy and avoiding side effect. Maintain drug levels in desired range.[5]

Various reasons for making SR
- It reduces the frequency of dosing.
- Increase effectiveness of the drug by localization at the site of action.
- Reducing the dose required. Providing the uniform drug delivery.[6]

Classification of rate-controlled drug delivery systems
Based on their technical sophistication –
Controlled drug delivery systems can be classified into
1. Rate– preprogrammed drug delivery systems.

2. Activation modulated drug delivery systems.
3. Feedback regulated drug delivery systems.
4. Site-targeting drug delivery systems.[7]

Advantages of Controlled Drug Delivery System

1. Reduction in frequency of intakes.
2. Uniform release of drug over time.
3. Its improved patient convenience and compliance due to less frequent drug administration.
4. More uniform effects.
5. Reduction in fluctuation in steady-state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
6. Increased safety margin of high potency drugs due to better control of plasma levels.
7. Maximum utilization of drug enabling reduction in total amount of dose administration.[8,9,10]

MATERIALS AND METHODOLOGY

Materials

Tab 1: List of material used for preparation of Hydrogel beads.

S. NO.	Chemicals	Manufacturer
1	Metformin hydrochloride	Newera scientific works, Meerut
2	Sodium Alginate	Loba chemie Pvt. Ltd.
3	Chitosan	HiMedia laboratories Pvt. Ltd.
4	Calcium Chloride	Central drug house, India
5	Acetic Acid	Qualigens Pvt. Ltd.
6	HPMC	Loba chemie Pvt. Ltd.

Instruments

Tab 2. List of Instruments used in formulation Preparations of Hydrogel Beads.

S. No.	Instruments	Specification
1	Analytical Weighing Balance	Citizenscale Pvt. Ltd.
2	Ultraviolet Visible Spectrophotometry	U.V-1800 Shimadzu, Japan
3	Infrared spectrophotometer	Iraffinity-1 Shimadzu, Japan
4	Dissoltion apparatus	Electrolab TDT-081Mumbai, India
5	Tray Dryer	NSW, India
6	ScanningElectron Microscope	LEO-430,Japan
7	Digital pH meter	Metler Toledo, Switzerland
8	X-ray Diffraction	Shimadzu- binary (.RAW)
9	Differentialscanning calorimetry	Diya labs

- **Preparation of hydrogel beads using Sodium alginate**

At first, sodium alginate (2.5%, 5%, 7.5%w/v) was dispersed uniformly in distilled water. During dispersion mixture it forms bubbles, for removing bubbles we leave it for some time. Metformin hydrochloride was added very slowly, to disperse the drug uniformly. The sodium-alginate drug dispersion was added dropwise via a needle fitted with a 10ml syringe into 100ml of 4% calcium chloride solution. After incubating for a predetermined time, the gelled beads were separated by filtration and washed with distilled water. Then the hydrogel beads were dried at 45^0 C**.**[11]

- **Preparation of hydrogel beads using Sodium alginate coated with Chitosan-**

Metformin hydrochloride microspheres were prepared by ionotropic gelation method using polymers like sodium alginate and chitosan, cross-linked with calcium chloride. Firstly, Sodium alginate with different ratio 2.5g, 5g and 7.5g was dissolved in purified water (100 ml). During dispersion mixture it forms bubbles, for removing bubbles we leave it for some time. The drug, Metformin hydrochloride (1g) was added to the polymer mixture and the resulting dispersion was added manually drop wise into concentration of varying calcium chloride solution (4%) and using different ratio of chitosan (0.5%, 1% and 1.5%) through a syringe with a needle size no. 18. The added droplets were retained in the calcium chloride solution for 30 min to complete the curing reaction. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with water and dried at 45^0 C.[12]

Note: After evaluating above three formulation it was observed that the percentage drug loading of drug was 50.2±0.1, 59.05±1.0 & 93±1 % for hydrogel beads prepared by using sodium alginate, using HPMC and sodium alginate & HPMC respectively. It was observed that drug loading was highest in hydrogel beads prepared by using sodium alginate coated with Chitosan. Hence hydrogel beads of sodium alginate coated with Chitosan were further used for optimization.

Central composite design (CCD)

Central composite design (CCD) was used to describe the relationship between the independent variables and the responses as well as to determine the drug loading

parameters for drug loaded micro-granules to reduce the number of trials which necessary to attain maximum numbers of information on product properties, and the screening was performed applying a 3^2 CCD.[13]

Tab 3. List of 3^2 Central composite design.

Batch code	Actual level of factor		Level of factor		
	Drug: Sodium Alginate	Chitosan(%)	Drug: Sodiuminate(%)	Chitosan (%)	$CaCl_2$(%)
R1	1:2.5	0.5	-1	-1	4
R2	1:5	1	0	0	4
R3	1:7.5	1.5	+1	+1	4
R4	1:2.5	1	-1	0	4
R5	1:5	1.5	0	+1	4
R6	1:7.5	0.5	+1	-1	4
R7	1:2.5	1.5	-1	+1	4
R8	1:5	0.5	0	-1	4
R9	1:7.5	1	+1	0	4
R10	1:5	1	0	0	4
R11	1:5	1	0	0	4
R12	1:5	1	0	0	4
R13	1:5	1	0	0	4

***Value expressed as mean±SD, n=3.**

RESULTS

- **Percentage yield**

The yield of hydrogel beads was determined by comparing the whole weight of beads formed against the combined weight of the copolymer and drug.

Tab 4. Data of percentage yield of hydrogel beads.

Batch code	Percentage yield
R1	70.16
R2	82.0
R3	91.18
R4	76.25
R5	85.32
R6	90.89
R7	76.12
R8	83.12
R9	90.78
R10	82.14
R11	85.56
R12	86.15
R13	84.61

- **Particle size analysis and morphology of hydrogel beads**

The particle sizes of the prepared hydrogel beads were determined by using Vernier calipers. Prepared hydrogel beads show that when the concentration of sodium alginate increases then the bead size behavior will be decreases. Color and shape of dried hydrogel beads of each batch was noted.

Tab 5. Data of Particle size analysis and morphology of hydrogel beads.
Drug entrapment efficiency (DEE).

Batch code	Color	Shape	ead size (mm)
R1	Brownish	Spherical	2.00±0.15
R2	Brownish	Spherical	1.98±0.01
R3	Brownish	Spherical	1.52±0.01
R4	Brownish	Spherical	2.19±0.
R5	Brownish	Spherical	1.92±0.01
R6	Brownish	Spherical	1.36±0.01
R7	Brownish	Spherical	2.22±0.02
R8	Brownish	Spherical	1.89±0.02
R9	Brownish	Spherical	1.26±0.01
R10	Brownish	Spherical	1.87±0.01
R11	Brownish	Spherical	1.85±0.01
R12	Brownish	Spherical	1.86±0.02
R13	Brownish	Spherical with tailing	1.84±0.02

***Value expressed as mean±SD, n=3.**

About 100 mg of accurately drug loaded microspheres were added into 100 ml of N HCl and the drug concentrations were determined spectrophotometrically at 232nm in UV- visible beam spectrophotometer. Prepared hydrogel beads show that when the concentration of sodium alginate increases then the DEE behaviour of hydrogel beads will be decreases.

Tab 6. Drug entrapment efficiency of prepared hydrogel beads Swelling index.

Batch coad	Drug entrapment effiency(%)
R1	93±1
R2	82±1.5
R3	79±1.5
R4	91±2.08
R5	81.19±1.51
R6	74.19±0.86
R7	92.16±1.53
R8	80.14±0.93
R9	71.20±0.16
R10	89.43±2.26
R11	87.17±0.58
R12	89.16±2.02
R13	86.14±1.85

***Value expressed as mean±SD, n=3.**

A Metformin hydrochloride bead of 100mg was weighed accurately. It was kept in a Petri dish and 50ml of 0.1 N HCl was added. The Petri dish was kept aside for 24 hrs. The weight of swollen matrix bead was measured. Prepared hydrogel beads show that when the concentration of sodium alginate increases then the swelling behavior of beads will be decrease.

Tab 7. Swelling index study of prepared hydrogel beads.

Batch code	Swelling index(%)
R1	193±1.5
R2	186±2.08
R3	179±2.08
R4	195±1.6
R5	184±1.8
R6	175±1.7
R7	199±1.9
R8	190±2.51
R9	185±1.5
R10	183±1.2
R11	186±1.7
R12	180±1
R13	179±1.5

***Value expressed as mean±SD, n=3**

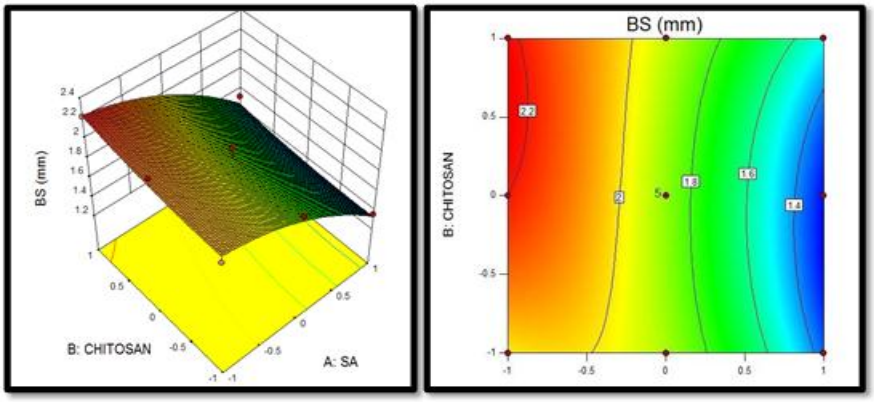
***In-vitro* release profile of Metformin hydrochloride beads**

The percentage drug released from sodium alginate beads containing Metformin hydrochloride in 8 h (R 8h %) was within the range of 82.19±0.25 (R13) to 70±0.49 (R1), and this was found to be lower with the increasing of both sodium alginate and Chitosan in the polymer-blend used shown in Table 15. In case of beads containing higher sodium alginate amount, the more hydrophilic property of sodium alginate binds better with water to form viscous gel-structure.

Tab 8. In-Vitro drug release data of Metformin Hydrochloride beads.

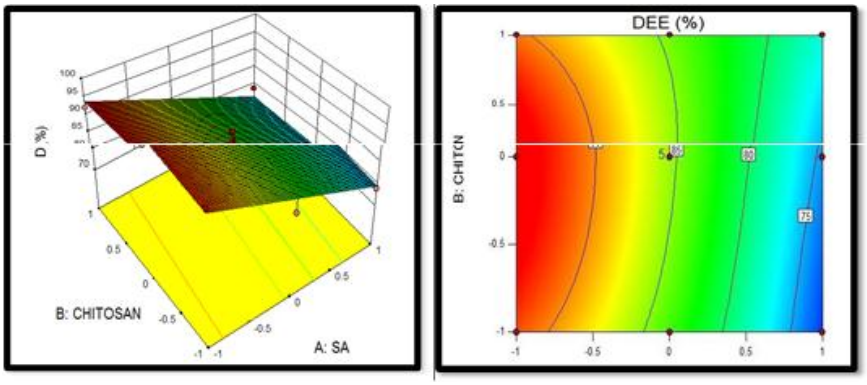
Time(hr)	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13
0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	38.22	45.38	49.1	39.92	46.23	47.94	40.27	46.52	50.50	45.23	48.25	49.26	44.27
1	41.16	49.39	57.9	42.19	50.35	55.24	45.95	51.30	59.31	50.56	55.23	57.59	59.59
2	44.12	51.71	65.4	45.50	52.27	63.38	47.93	53.69	69.87	53.6	57.54	52.62	55.62
3	51.89	54.38	71	52.28	55.36	69.24	51.25	56.32	73.67	55.39	59.37	56.38	57.38
4	53.89	61.50	75.4	57.64	62.4	74.08	54.94	62.49	77.67	61.62	63.50	63.50	64.52
5	59.63	65.59	79.84	61.68	66.38	77.93	62.40	66.38	81.66	65.2	68.92	64.93	69.939
6	65.43	74.82	84.47	67.03	75.49	81.45	69.57	76.4	86.20	75.23	77.30	76.31	74.32
7	68.10	82.73	86.02	71.57	83.98	83.62	76.08	85.23	89.05	83.2	82.22	80.30	81.31
8	70	85	88.1	76	85.76	89.48	78	87.26	90.84	84.51	84.78	83.17	82.19

Response Surface Analysis- The 3-dimensional response surface graphs were generated by the design expert 10.0.6 software. The 3D response surface graph related to bead size shown in Fig, It Indicates that increasing of sodium alginate concentration then decreasing of bead size concentration. Hydrogel beads containing Metformin hydrochloride by ionotropic gelation technique. However, concentration of sodium alginate increases then concentration of DEE will be decreases. It indicated by the three-dimensional response surface graph relating release shown in Fig. 2, and increasing the concentration of sodium alginate then also increasing the concentration of DR8h shown in Fig. 3.



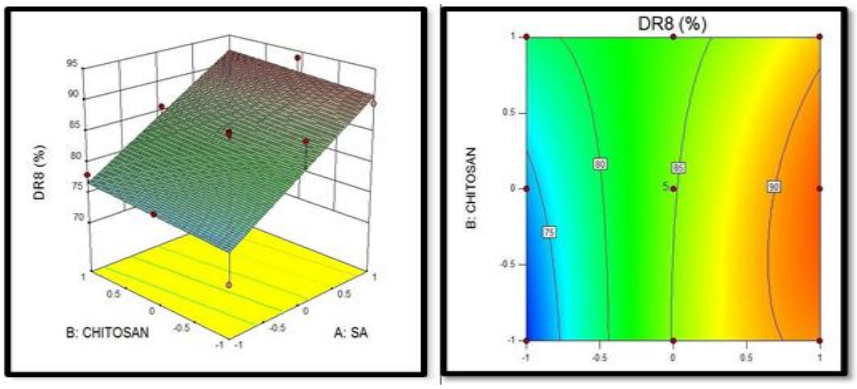
(a) **(b)**

Fig. 1: Response surface and counter plot for bead size (a, b).



(a) **(b)**

Fig. 2: Response surface and counter plot for DEE (a, b).



(a) **(b)**

Fig no. 3: Response surface and counter plot for Drug release (a, b).

Optimization

The product will be optimized by using Central composite designs. Central composite design is a most useful approach in the development and optimization of drug delivery device. The influences of main effects (factors) on responses here (DEE, drug release and bead size) were further elucidated by response surface methodology. The objective of the central composite design is to understand a model as fully as possible the effect of factors and their levels, over the whole of the experimental design, and to predict the response inside the design. Moreover, it can be used for optimizing a formula (i.e., maximizing one or more of the responses, keeping the formulation variable setting within a satisfactory range), carrying out simulations with the model equations and plotting the responses. Overlay plot of variable response were analyzed after filling desirable criteria shown in Table 9, then we find the graph of overlay plot, then added the flag on particular place and note down the reading of all response. here (DEE, drug release and particle size), shown in Fig. 2 and Fig. 3.

Tab 9. Desirable criteria range for optimized batch as per design expert.

S. No.	Constraints name	Lower limit	Upper limit
1	Bead size	1.26	2
2	DEE	85	93
3	DR8h	85	93.84

Validation of optimized batch

The check point variables all the predicted and observed value show in Table 10. The optimized Chitosan SA beads containing Metformin hydrochloride VC1 (optimized batch), VC2, VC3 and VC4 was evaluated for Bead Size (MM), DEE (%) and R 8h (%). The results of experiments done with predicted responses by the mathematical model and those actually observed.

Tab 10. Validation checkpoint compositions and their results.

Check point batch	X1 (amount in mg)	X2 (amount in mg)	Response variables	Predicted values	Observed values	%error
VC1	-0.047	0.963	BS (mm)	1.995	1.989	0.302
(Optimized	(3.825)	(1.48)	DEE (%)	85.507	85.548	-0.047
batch)			DR8h (%)	84.154	84.148	0.007
VC2	-0.091	- 0.085	BS (mm)	1.904	1.909	-0.262
	(4.775)	(0.96)	DEE (%)	84.995	84.987	0.009
			DR8h (%)	82.911	82.9	0.013
VC3	-0.431	- 0.252	BS (mm)	1.997	1.994	0.150
	(3.925)	(0.875)	DEE (%)	87.791	87.782	0.010
			DR8h (%)	80.080	80.01	0.087
VC4	-0.183	- 0.966	BS (mm)	1.07	1.913	-0.313
	(4.55)	(0.52)	DEE (%)	85.045	85.03	0.017
			DR8h (%)	81.427	81.42	0.008

DISCUSSION

Oral controlled release of Metformin hydrochloride beads can be achieved by ionotropic gelation techniques by using sodium alginate coated with chitosan respectively. Compressibility study and angle of repose of hydrogel beads was found to be in the range of 8.8±0.2 to 6.1±0.16 & 18.80±0.015 to 24.51±0.020 hence it is concluded that it has good and excellent flow characteristics respectively.

Percentage yield was found to be in the range of 91.18 to 70.16%. Swelling characteristics of hydrogel beads were decreased when concentration of sodium alginate was increased. Surface smoothness, circular shape of the Metformin hydrochloride beads was increased by increasing the polymer concentration, which was confirmed by SEM. The mean particle size of Metformin hydrochloride beads was decreased when the concentration of sodium alginate was increased, beads size was found to be in the range 2.22±0.02 to 1.26±0.01. Metformin hydrochloride beads with normal frequency distribution were obtained. Entrapment efficiency was decreased with increase in the polymer concentration, found to be range 93±1 to 71.20±0.16. (Higuchi's classical diffusion), Log cumulative percentage drug release Vs log Time (Peppa's exponential). The kinetics data results are shown in Table 16. When the drug release data was put in to Higuchi's equation, good correlation coefficient (r) values 0.9274 to 9716 were obtained, indicating the drug release was diffusion-controlled release mechanism.

Optimizations of formulated hydrogel beads were done by using 3^2 CCD. The outcomes for response parameters, that is, beads size, DEE and DR8h were subjected to regression analysis and statistical models were found to be significant. Observed responses, beads size, DEE and DR8h indicate good relation between the dependent and independent variables. The beads size, DEE and DR8h for all thirteen batches (R1 to R13) showed a wide variation (i.e., 1.26- 2.22 mm, 71.20-93% and 70-90.84% respectively).

Validation of optimized batch was done by formulating four different batches by considering the optimum value as found in overlay plot as shown in Figure 2, and 3, and by the comparison of observed values with the predicted responses, it was observed that models were found to be valid and showed close agreement. Optimized batch was found (VC1). Optimization of formulated beads was done by 3^2CD.

CONCLUSION

Pre-formulation studies of pure drug like pH, melting point, solubility, and FTIR and UV analysis of Metformin hydrochloride were complied with IP standards. Oral controlled release of Metformin hydrochloride beads can be achieved by ionotropic gelation techniques by using sodium alginate coated with chitosan respectively. SEM, XRD and DSC were useful in the evaluation of beads. As the drug to polymer ratio was increased, the mean particle size of Metformin hydrochloride microspheres was decreased. Metformin hydrochloride microspheres with normal frequency distribution were obtained. Entrapment efficiency decreases with increase in the polymer concentration. Increasing the concentration of sodium alginate then also

increases the concentration of releaseof hydrogel beads. Optimized batch was found by 3^2 central composite design.

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