WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 16, 985-995. Research Article ISSN 2277–7105

PREPARATION AND EVALUATION OF PRELIMINARY MICROSPHERES USING PECTIN AND XANTHAN GUM POLYMERS

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Article Received on
01 August 2023,

Revised on 22 August 2023,
Accepted on 12 Sept. 2023

DOI: 10.20959/wjpr202316-29689

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ABSTRACT

This work is aimed to design blank microspheres using natural polymers such as pectin, and xanthan gum in order to achieve controlled release. The microspheres were prepared by ionotropic gelation method using different ratios of sodium alginate-pectin, and sodium alginate-xanthan gum polymers. The blank microspheres were prepared to understand the morphological characteristics and physicochemical properties. Microspheres were subjected to different evaluation parameters such as morphology, percentage yield, flow properties are the angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, particle size, and swelling index. The prepared microspheres are spherical in shape, and show good flow properties and pH-dependent swelling was seen, indicating that water intake was low in an acidic medium and elevated in an alkaline medium pH. The successful development of blank microspheres using natural polymers. These preliminary results indicate microspheres can represent a valid carrier for controlled drug delivery of drug.

KEYWORDS: microspheres, pectin, xanthan gum, sodium alginate, and pH-dependent.

INTRODUCTION

Microspheres are small spherical particles ranging in size from 1 to 1000 µm that are used in the controlled delivery of drugs. The oral controlled drug release using hydrophilic polymers in multiple dosage forms which aids in the uniform and prolonged release of drug.[1,2]

Controlled-release drug delivery systems make an effort to maintain drug blood concentration at relatively consistent and efficient levels in the body through placement or timing of administration. In order to reduce blood level changes, minimize drug accumulation, use less total drug, enhance patient compliance, and minimize both local and systemic side effects, CRDDS offer a number of benefits.[3]

Sodium alginate is an anionic polysaccharide, the primary polymer, was achieved with oppositely charged counter ions i.e., Ca^{++} to form microspheres which were further sustained by using divalent polymer.[4,5] Pectin is a non-starch, linear polysaccharide of mainly α-(1–4)-linked D-galactouronic acid residues interrupted by 1,2-linked L-rhamnase residues. Pectin is water soluble, Pectin is employed in a number of pharmaceutical, cosmetic, food, and biological applications due to its biocompatibility, biodegradability, and non-toxicity.[6,7,8] Xanthan gum (XG) is a high molecular weight, anionic extracellular polysaccharide that is produced by the gram-negative bacterium Xanthomonas campestris. It is widely used in food, cosmetics, and pharmaceuticals because of its encouraging reports on safety.[9, 10]

MATERIALS AND METHODS

Pectin, calcium chloride, potassium dihydrogen phosphate (SDFCL (SD of fine-chem Ltd., Mumbai) xanthan gum, sodium dihydrogen orthophosphate, hydrochloric acid (NICE Chemicals (P) Ltd).

METHODOLOGY

Before drug loading into microspheres, preliminary studies were conducted on microspheres. So, a blank preparation is done on microspheres.

Preparation of pectin microspheres

Pectin microspheres were prepared by ionotropic method. Pectin was weighed accurately according to composition added 100 ml of water and placed for stirring up to 30 mins, using a mechanical stirrer, for a homogenous solution. prepared the calcium chloride solution. Pectin homogenous solution was added dropwise into $cacl_2$ solution using a syringe, leaving for 30 minutes to 1hr for hardening, and then filtered and placed for air drying and collected the dried microspheres.

Table no.1: Pectin calcium chloride beads.

Sl. No	Formulation	Pectin(gm)	Crosslinker (calcium chloride) (gm)
1	P1	1	2
2	P2	2	4
3	P3	4	2
4	P4	4	10

Preparation of sodium alginate- pectin blank microspheres

The modified method of Sreejan Manna et al[11], and the $cacl_2$ is used as a cross-linker and the processing variables, such as the drying process and stirring speed, differ from it.

Sodium alginate and pectin were weighed accurately according to composition added 25 ml of water and placed for stirring up to 30 mins, using a mechanical stirrer, for a homogenous solution prepared the calcium chloride solution. Sodium alginate-pectin homogenous solution was added dropwise into $cacl_2$ solution using a syringe, leaving for 30 minutes for hardening, and then filtered it and placed for air drying and collected the dried microspheres.

Table no.2: Sodium alginate-pectin blank microspheres.

SL. No	Formulation	Sodium alginate (mg)	Pectin (mg)	Crosslinker (Calcium chloride)
1	F1	900	100	2.5%
2	F2	800	200	2.5%
3	F3	700	300	2.5%
4	F4	600	400	2.5%
5	F5	500	500	2.5%
6	F6	400	600	2.5%
7	F7	250	750	2.5%

Preparation of sodium alginate- xanthan gum blank microspheres

Sodium alginate and xanthan gum were weighed accurately according to composition added 25 ml of water and placed for stirring up to 30 mins, using a mechanical stirrer, for a homogenous solution prepared the calcium chloride solution. Sodium alginate- xanthan gum homogenous solution was added dropwise into calcium chloride solution using a syringe, leaving for 30 minutes for hardening, and then filtered it and placed for air drying and collected the dried microspheres.

Table no.3: Composition of sodium alginate-xanthan gum microspheres.

SL. No	Formulation	Sodium alginate(mg)	Xanthan gum(mg)	Crosslinker (calcium chloride)
1	X1	900	100	2.5%
2	X2	850	150	2.5%
3	X3	800	200	2.5%
4	X4	750	250	2.5%
5	X5	700	300	2.5%
6	X6	650	350	2.5%

EVALUATION PARAMETERS

Morphology of microspheres

The prepared microspheres were all visually examined for colour and size uniformity.

Percentage yield (%)

The prepared microspheres were weighed and the weight of the microspheres was divided by the amount of polymer used. It is calculated by following the formula.[12]

$$\text{percentage yield}(\%) = \frac{\text{pratical yield}}{\text{theoretical yield}} \times 100$$

Flow properties

Angle of repose

The angle of repose measures the flow characteristics. The angle of repose was determined by using the funnel method. In this method, a funnel was secured with its tip at a 1cm height above the paper and placed on a flat horizontal surface. Microspheres were carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. Measure the height of the heap pile and the radius of the base with a ruler. The angle of repose was determined by using the equation.[13]

$$\tan\theta = \frac{h}{r}$$

Bulk density and tapped density

Accurately weighed 1g of microspheres were poured into a 10ml measuring cylinder and the initial volume was observed and volume is noted and the cylinder was tapped continuously up to 100 times and noted the tapped volume.it is expressed in gm/ml and calculated by using the given formula.[14]

$$BD = \frac{\text{Weight of the powder}}{\text{Initial volume}} \qquad TD = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Carr's index

The compressibility of the granules is determined by Carr's compressibility index.it is indirectly related to the relative flow rate cohesiveness. it was calculated by using the results of bulk density and tapped density. Calculated by using the given formula.

$$\text{Carr's index (\%)} = \frac{\text{TD} - \text{BD}}{\text{TD}} \times 100$$

Hausner's ratio

Hausner's ratio was related to interparticle friction. It was also calculated by using the results of bulk density and tapped density.

$$\text{Hausner's ratio} = \frac{\text{TD}}{\text{BD}}$$

Particle size analysis

Particle sizes of microspheres were determined by optical microscopy. The optical microscope was fitted with an eyepiece micrometre which was then calibrated with a stage micrometre previously. About 50 microspheres were randomly selected from each formulation and then the average size was calculated.[15]

Swelling index

0.1g of microspheres were added into 100 ml of PH 1.2 Hcl buffer and PH 6.8 phosphate buffer solution and allowed to stand for 2 hours and then filtered the solution and weighed the microspheres and calculated by using the equation.

$$\text{swelling index} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

Statistical analysis

Experimental data were expressed as the mean value ±S.D. Statistical analysis was performed using the normality test and one-way analysis of variance (ANOVA) test using a graph pad prism (version 5, GraphPad Software, San Diego, California, USA). Differences were considered to be statistically significant when $p < 0.05$ for ANOVA and while normality test is well accepted for the above formulations at a level of significance of 5 percent.

RESULTS AND DISCUSSION

Pectin calcium chloride microspheres

Blank pectin calcium chloride microspheres were prepared with different concentrations (P1, P2, P3, P4) .P1 and P2 show flat shape and smooth texture. During the curing period, microspheres sink into the bottom and after 10min they adhere to each other. P3 and P4 shows irregular shape and curing time is above 1 hour. P3 microspheres were observed to adhere to each other after filtration. P4 was filtrated and placed for air drying in this process microspheres were changing their shape slowly. due to its smooth texture. so pectin calcium chloride beads are unsuccessful.

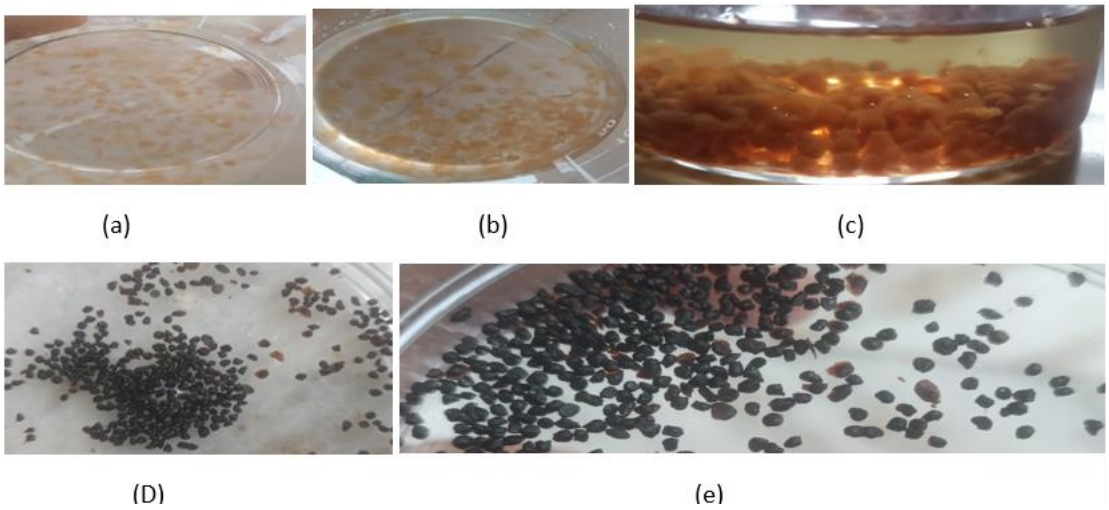

Figure no:1 (a) P1 formulation (b) P2 formulation (c) P4 formulation (d) (e) dried P4 microbeads.

To overcome it sodium alginate was added in different quantities.

Blank sodium alginate-pectin and sodium alginate-xanthan gum microspheres

Increasing the pectin concentration more than the prepared concentrations leads to the softening of microspheres. The concentration of xanthan gum increased than prepared concentration viscosity was increased and so hard to extrude from a syringe.

Percentage yield

The percentage yield of sodium alginate-pectin microspheres ranges from 98% to 93% and the percentage yield of sodium alginate-xanthan gum microspheres ranges from 96% to 92%. The values given in table no 4.

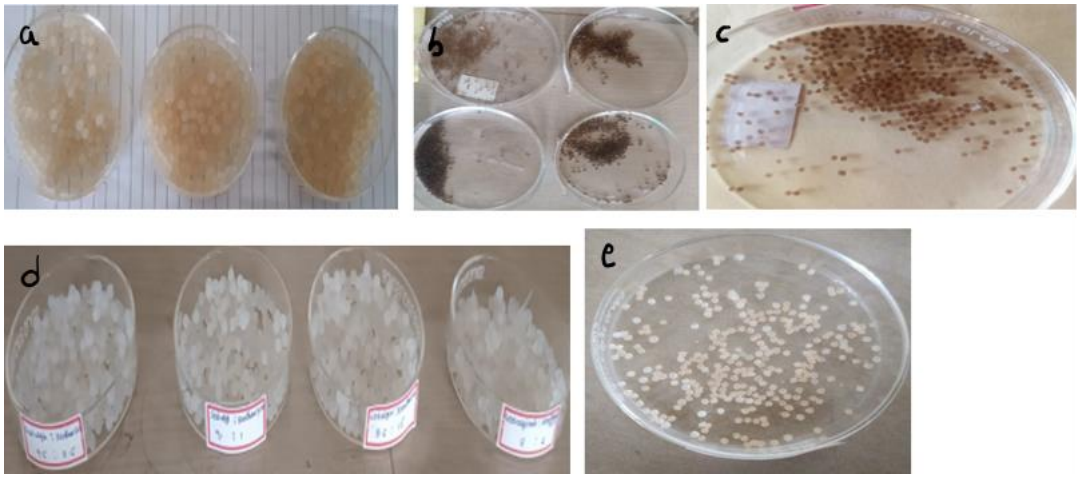

Figure no: 2 (a) before drying of sodium alginate-pectin microspheres (b)(c) dried sodium alginate-pectin microspheres (d) before drying of sodium alginate-xanthan gum microspheres (e) dried sodium alginate-xanthan gum microspheres.

Table no.4: Percentage yield and Appearances of microspheres.

S. No	Formulation	Percentage yield (%)	Appearances of beads
1	**F1**	93%	Goldish brown, Spherical
2	**F2**	93%	Goldish brown, Spherical
3	**F3**	95%	olive colour, Spherical
4	**F4**	94%	olive colour, Spherical
5	**F5**	92%	Brown, Spherical
6	**F6**	97%	Brown, Spherical
7	**F7**	98%	Brown, Spherical
8	**X1**	92%	Pale white, Spherical
9	**X2**	93%	Pale white, Spherical
10	**X3**	95%	Pale white, Spherical
11	**X4**	96%	Pale white, Spherical
12	**X5**	93%	Pale white, Spherical
13	**X6**	96%	Pale white, Spherical

Flow properties

Microspheres show excellent flow properties. The angle of repose was found to be less than 20 which indicates good flow. The bulk density of all formulations was found to be in the range of 0.7 to 0.59gm/ml, and the tapped density was observed between 0.77 to 0.68 gm/ml. the values for the compressibility index and Hausner's ratio were calculated. The values for the compressibility index were found between 4.1 and 17.4%. The values for Hausner's ratio were found in between 1.04 to 1.16. Overall, these values indicate good flowproperties. The results are given in the below table no 5.

Table no.5: Flow properties of microspheres.

Formulation	Angle of repose(°)	Bulk density g/ml	Tapped Density g/ml	Carr's index	Hausner's ratio
F1	11.4±0.25	0.5921±0.16	0.6821±0.13	13.19	1.15
F2	6.16±0.15	0.612±0.34	0.7012±0.14	12.7	1.14
F3	14.1±0.13	0.5925±0.23	0.6844±0.48	13.1	1.15
F4	19.2±0.50	0.6391±0.23	0.7121±0.43	10.25	1.11
F5	13.74±0.18	0.551±0.13	0.6023±0.14	8.5	1.09
F6	10.7±0.32	0.6041±0.12	0.630±0.19	4.1	1.04
F7	17.4±0.19	0.595±0.13	0.7210±0.43	17.47	1.16
X1	18.41±0.25	0.7263±0.52	0.7666±0.17	5.26	1.055
X2	16.10±0.38	0.6772±0.33	0.7095±0.28	4.2	1.04
X3	13.83±0.11	0.7±0.41	0.7768±0.20	9.09	1.10
X4	16.44±0.45	0.6809±0.16	0.7150±0.57	4.2	1.05
X5	13.0±0.20	0.6545±0.47	0.72±0.36	9.1	1.10
X6	15.16±0.13	0.6565±0.19	0.6863±0.29	4.3	1.04

Mean ± S.D n=3

Particle size

The particle size of sodium alginate-pectin range from 1121 to 926 µm and the particle size of sodium alginate-xanthan gum range from 1134 to 966 µm. the value is given in table no 6.

Swelling index

The swelling study results are in Table no 6, it is clearly shows that the swelling of the microsphere increases with time. The swelling rate of phosphate buffer (PH 6.8) is higher than the acidic buffer (PH 1.2).

Table no.6: particle size and swelling index of microspheres.

S. No	Formulation	Mean particle size (µm)	Swelling index	
			In acidic (Hcl) buffer	Phosphate buffer
1	**F1**	990±0.65	90±0.21	1445±0.81
2	**F2**	926±0.11	60±0.12	1217±0.76
3	**F3**	953±0.13	99±0.12	1450±1.12
4	**F4**	978±0.46	90±0.72	1400±0.94
5	**F5**	1001±0.74	100±0.38	1456±1.08
6	**F6**	981±0.21	120±0.79	1585±1.23
7	**F7**	1121±0.55	190±0.15	1890±1.98
8	**X1**	966±0.84	90±0.13	1450±1.14
9	**X2**	973±0.11	93±0.15	1200±0.98
10	**X3**	1073±0.42	99±0.11	1440±1.2
11	**X4**	987±0.64	100±0.19	1235±1.13

12	**X5**	998±0.32	120±0.78	1486±1.23
13	**X6**	1134±0.13	140±0.79	1770±1.87

Mean ± S.D n=3

Statistical analysis

Blank microspheres prepared by using pectin and xanthan gum were subjected to one-way ANOVA and normality tests using Graph pad prism. The statistical analysis of one-way ANOVA produces a p-value that tends to be <0.0001. At the same time, the normality test is well accepted for all formulations at a significance level of <0.05%.

CONCLUSION

Blank microspheres were designed using natural polymers such as pectin and xanthan gum. The microspheres were prepared using the ionotropic method. In the first batch of pectin calcium chloride, microspheres were inefficient due to their soft texture so, sodium alginate was added. The sodium alginate-pectin and sodium alginate-xanthan gum blank microspheres were developed successfully. Microspheres were subject to evaluation parameters such as the morphology of microspheres are spherical in shape. Both microspheres showed good Flow properties, mean particle size varying from 1121µm to 926µm for sodium alginate-pectin and the mean particle size of sodium alginate-xanthan gum varying from 1134 µm to 966 µm. The swelling study showed a swelling rate reaching 190% in the acidic buffer(pH 1.2) and 1890% in the phosphate buffer (pH 6.8) in sodium alginate-pectin microspheres and in sodium alginate-xanthan gum showed 140% in acidic buffer and 1770% in phosphate buffer. All blank microspheres exhibited satisfactory results. Blank microspheres are suitable as drug carriers exhibited satisfactory results.

FUTURE SCOPE

Further, using the formulation of the blank microspheres the drug-loaded (vildagliptin) microspheres can be formulated and evaluated for various evaluation parameters. I have selected vildagliptin as a model drug for this due to the short half-life of the drug.

ACKNOWLEDGEMENT

I would like to thank my guide Dr. M. KRISHNAVENI, M.Pharm., Ph.D., principal Dr. K. HARINADHBABA, M.Pharm., Ph.D., MBA. Director, Dr. AVS. PRASAD, and staff of Narayana Pharmacy College for their support during this research work.

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