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FORMULATION DEVELOPMENT OF NATURAL SUGARS CROSSLINKED GELATIN MICROSPHERES OF PARACETAMOL

***Garima Verma and Manoj Kumar Mishra**

*Shambhunath Institute of Pharmacy, Jhalwa, Allahabad, Uttar Pradesh-211012, India.

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***Corresponding Author**
Garima Verma
Shambhunath Institute of Pharmacy, Jhalwa, Allahabad, Uttar Pradesh-211012, India.

ABSTRACT

The present study aimed to investigate the ability of native sugars (e.g. glucose, fructose, galactose and sugar) to induce cross-linking of gelatin for the preparation of modified release microspheres of paracetamol. The microspheres were prepared by emulsion cross-linking method and they were evaluated for *in vitro* drug release and drug content. The result of *in vitro* studies revealed that as the degree of cross-linking increases, the percentage drug release decreases. It was found that fructose had shown maximum drug release as compared to glucose, galactose and sucrose in drug: polymer ratio 0.5:1 due to the lesser cross linking. The microspheres cross-linked with fructose showed highest drug content. The study also shows that pure drug had maximum percentage of drug release due to the absence of cross linking. The result suggests that native sugars could be an interesting agent to cross-link gelatin for obtaining modified release of Paracetamol from the microspheres.

KEYWORDS: Microspheres, Cross-Linking, Gelatin, Native Sugars.

INTRODUCTION

Recent research efforts throughout the world have resulted in significant development of novel drug delivery systems. Among these systems, microspheres have emerged as an attractive dosage form due to the advantages it offers like effective taste masking, improvement of flow, safe handling and good sustained drug release properties.[1] Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm.[2] After considering properties desirable for degradable polymer matrix, gelatin was selected especially because it is natural and nontoxic. Gelatin is extensively used in

pharmaceutical industries due to its film forming properties.[3-5] Gelatin suffers from the main drawback that it dissolves rapidly in aqueous environments, making the use of the polymer difficult for the production of long-term delivery systems. This adverse aspect requires the use of a cross-linking agent in forming nonsoluble networks in microspheres. However, the use of cross-linking agents such as formaldehyd[6] and glutaraldehyde[7,8] can lead to toxic side effects owing to residual cross-linkers.

In this respect, alternative methods such as thermal hardening treatment[9] or natural cross-linkers, such as dextran[10] or sugars[11] have been tried for the preparation of gelatin devices. The thermal hardening treatment is time consuming and it is unsuitable for thermolabile drugs. Another study was reported that native or oxidized dextran could reduce the solubility of gelatin and sustain the release of model drugs such as sodium cromoglycate from gelatin microspheres.[12] In another study investigated, the crosslinking ability of native and oxidized mono and disaccharides (glucose, fructose and sucrose)[13] were depicted. The investigators concluded that oxidized sugars could be interesting agents to crosslink with gelatin. The authors proposed the possible mechanism involved in gelatin cross-linking by aldose sugars. The objective of this work was to obtain an optimized sugar cross linked gelatin based paracetamol microspheres.

MATERIALS AND METHOD

Paracetamol and d-glucose, received as gift sample from Merck (India) Ltd. Fructose, sucrose, galactose and acetone obtained from Qualigens Fine Chemicals, Mumbai. Gelatin (SD fine chemicals limited, Mumbai), Lquid paraffin (CDH laboratory reagent, New Delhi). Isopropanolol (Qualigens Fine Chemicals, Mumbai) were purchased.

Method of Preparation of Gelatin Microspheres

The microsphere was prepared by emulsion crosslinking method. 15% w/v of gelatin solution (80^0C) was taken and to this add 1.5g of aldose sugar (glucose, fructose, sucrose and galactose). Then Paracetamol was added to the solution of gelatin and sugar. The resulting mixture was added to liquid paraffin solution (15% w/v) having 1.5% w/v tween 80 at 80^0C with constant high stirring (550-850 rpm) for 2 h. Rapid cooling to 5^0C using an ice-bath to harden the gelatin capsule. Then 15 ml of isopropanolol was added (0.5×4 ml, 5^0C) at regular intervals to dehydrate droplets. Stirring was continued for 2h, followed by filtration. The microspheres were washed with isopropanolol to remove the adhered oil. Then the dried microspheres were taken (100mg equivalent of Paracetamol), filled in hard gelatin capsule.

The microspheres prepared with glucose, fructose, galactose and sucrose crosslinked with gelatin in 0.5:1 and 1:1 ratio each.

***In Vitro* Dissolution Study**

Microspheres equivalent to 100mg filled in hard gelatin capsules were evaluated for *in-vitro* dissolution study. The study was carried out in accordance with the USP 24 type I rotating basket apparatus (HICON, Delhi) using 900 ml phosphate buffer (pH 7.4, 37±0.5^0 C) at 50 rpm. A muslin cloth (200#) was tied over the basket to prevent slippage of microspheres from the basket. Samples of 5ml were withdrawn at regular time intervals and replaced with same volume of fresh media, filtered and analyzed spectrophotometrically (Shimadzu 1600) at 260.5nm for cumulative drug release.

Drug Content

The microspheres were evaluated for drug content. Drug loaded microspheres (100 mg) were powdered and suspended into 100 ml phosphate buffer (pH 7.4). The resultant dispersion was exposed to ultrasonic treatment (4-5 h) and filtered. The drug content was determined pectrophotometrically (Shimadzu 1600) at 260.5 nm.

RESULT AND DISCUSSIONS

It was found that maximum percentage of drug release was by fructose in drug: polymer ratio (1:1) and least percentage of drug release in case of sucrose (1:1) ratio. Fig: 1 shows that percentage drug releases of all formulations with different ratios were found below as compared to that of the pure drug. Order of percentage drug release for 0.5:1 ratio formulations were in following order: pure drug > glucose > fructose > sucrose > galactose and in case of 1:1 ratio is: fructose > pure drug > glucose > sucrose > galactose. The nature and quantity of sugar had direct effect on the nature of cross-linking and higher the cross-linking higher will the drug entrapment and lesser will be the drug release. It can be assured that fructose in 1:1 shows maximum drug release which could be due to lesser degree of cross-linking. The pure drug release was maximum due to absence of cross-linking. The solubility of gelatin was reduced because of addition of native sugars and cause sustaining effect in release of drug. Faster drug release was expected from water soluble crosslinking gelatin. The result showed that minimum percentage of drug release in sucrose when we use drug: gelatin (1:1) (Fig: 2). The maximum release in case of fructose may be due to number of molecules of gelatin participate in crosslinking will be less in case of fructose while in case of sucrose number of crosslinking will be more which forms dense insoluble matrix, reducing

burst effect and decrease the release of drug gelatin. Maximum percentage yield was obtained in case of fructose (1:1) with 86% (Table: 1).

Table: 1 Comparative chart of percentage yield and Drug content in 10mg microsphere in different formulation

Sugar	Paracetomol: Gelatin ratio	Yield (mg)	% Yield	Drug content in 10 mg microsphere (mg)
Fructose	0.5:1	610	37.53	4.1
	1:1	1720	86.00	4.9
Glucose	0.5:1	620	38.15	3.09
	1:1	950	47.5	3.81
Galactose	0.5:1	870	53.53	5.5
	1:1	370	18.5	6.2
Sucrose	0.5:1	470	28.92	2.6
	1:1	470	23.5	3.2

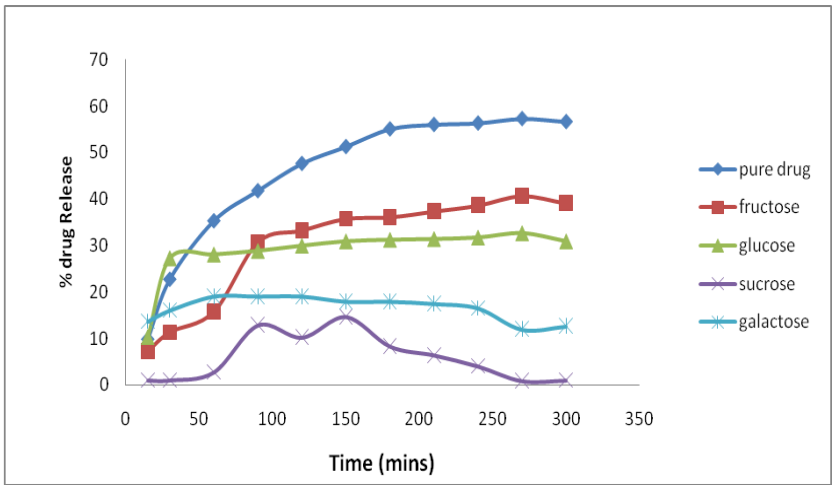

Fig 1: Comparative % drug release profile of paracetamol with different sugars crosslinked with gelatin of 0.5:1 ratio

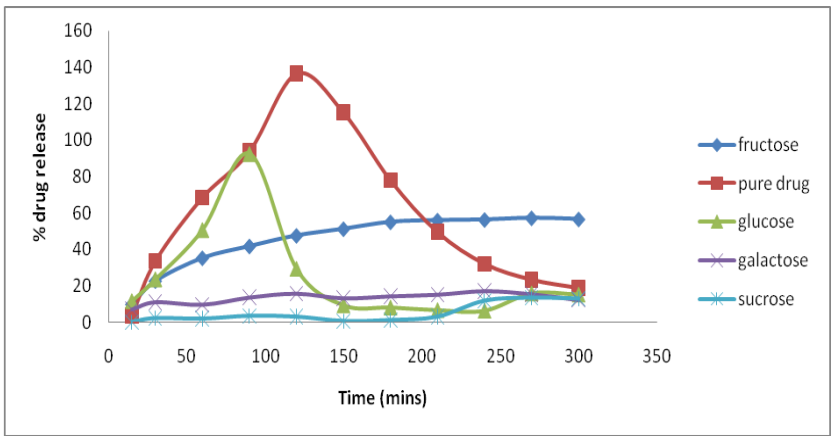

Fig 2: Comparative % drug release profile of paracetamol with different sugars cross-linked with gelatin of 1:1 ratio

CONCLUSION

The results revealed that gelatin microspheres containing paracetamol could be successfully prepared using native sugars (fructose) as cross-linking agent. The parameters such as amount of sugar, concentration of gelatin, drug to gelatin ratio should be critically controlled. It is concluded that higher the cross-linking concentration with sugar higher the drug entrapment and lesser will be the drug release. The maximum drug release is shown by fructose due to lesser degree of cross-linking.

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