Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 3, 2013

Research Article

FORMULATION AND EVALUATION OF THIOCOLCHICOSIDE MUCOADHESIVE MICROSPHERES

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Received: 28 Jun 2013, Revised and Accepted: 06 Aug 2013

ABSTRACT

The objective of this study was to develop mucoadhesive microspheres of Thiocolchicoside for management of pain. Thiocolchicoside has short mucological half-life (6hr), high first-pass metabolism and poor mucoavaibility (25%). So, in order to improve the mucoavailability and efficacy, Mucoadhesive microspheres are prepared by ionotropic gelation technique using Sodium alginate and mucoadhesive substance like Chitosan and Carbopol 934p. Nine different formulations (F1-F9) were prepared by using various formulation variables. The microspheres have been characterized invitro in the terms of their surface morphology, particle size, encapsulation efficiency, swelling ratio and mucoadhesivity. Almost spherical microspheres were obtained with sufficient swelling and Mucoadhesive property. Among all the 9 formulations the F9 has Entrapment Efficiency of 92.55 % , swelling factor of 95.4%,80% muco adhesion invitro drug release profile showed of 93.89% drug release for 12 hrand Mean population diameter of 375±1.27.From the results obtained it is concluded that F9 formulation had good release properties and considered as best formulation.

Keywords: Thiocolchicoside, Sodium alginate, Ionotropic gelation, Carbopol 934p, Chitosan and Microspheres.

INTRODUCTION

Thiocolchicoside (TCC) is a semi synthetic sulfur derivative of colchicoside, a naturally occurring glucoside present in the plant Gloriosa superba. TCC has been used clinically for more than 35 years as a muscle-relaxant, anti-inflammatory, and analgesic drug[1].

Despite tremendous advancement in drug delivery, oral route remains the preferred route for the administration of therapeutic agents,

- Low cost of therapy
- Ease of administration
- Higher levels of patient compliance.

Microsphere [2]carrier systems made from the naturally occurring mucodegradable polymers have attracted considerable attention for several years in sustained drug delivery [3]. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. This can be achieved by coupling mucoadhesive characteristics to microspheres and developing mucoadhesive microspheres. The term mucoadhesion describes materials that bind to the mucological substrates such as mucosal membranes. Adhesion of mucoadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of absorption. This prolonged residence time can result in the enhanced absorption and in combination with a controlled release [4,5]of drug, also improved patient compliance by reducing the frequency of administration. The epithelial adhesive properties of mucin have been applied in the development of gastro retentive drug delivery systems.

Thiocolchicoside is a muscle relaxant with anti-inflammatory and analgesic effects. It acts as a competitive GABA-A receptor antagonist and also inhibits glycine receptors with similar potency. Thiocolchicoside binds to GABA-A and strychnine sensitive glycine receptors Thiocolchicoside is having some of the side effects like somnalescence, weight gain, bone pain and the common side effects may include nausea, dizziness, stomach pain and diarrhea [6,7].

In this study thiocolchicoside, was chosen to be microencapsulated by the ionotropic gelation technique using sodium alginate [8] and chitosan blend and Carbopol 934 p.The proposed system is expected to provide several advantages. Firstly, gelation of the aqueous solution of alginate/chitosan/Carbopol 934p blend renders oral sustained drug delivery. Gastric retention time of microspheres enhances with the addition of mucoadhesive agent, resulting in the delivery of drug across the mucous membrane for an extended period of time in intestine.

So, the main aim of the present work was to prepare microspheres containing thiocolchicoside by ionotropic gelation [9]technique and is to have sustained effect of the drug.

MATERIALS AND METHODS

Materials

Thiocolchicoside was obtained from VKT Pharma limited, Vishakhapatnam. The polymers Sodium alginate, carbopol 934p,calcium chloride and Chitosan were obtained from Karnataka Fine Chem. Pvt.Ltd (Bangalore).All other solvents used were of analytical grade.

Preparation of mucoadhesive microspheres

Accurately weighed about 0.7gm of sodium alginate (as given in table -1 for individual formulations) and kept aside, then it was dispersed in 50ml of distilled water by using magnetic stirrer at 40^0C.Then after complete dispersion, added accurately 0.5gm of thiocolchicoside then the stirring was continued until complete and uniform dispersion was obtained. Then the chitosan[9] solution was prepared by dispersing the 5mg of chitosan powder in 10 ml of distilled water by heating at 40^0 C .Then the above prepared chitosan solution was added to the homogenous dispersion of sodium alginate containing drug which was homogenized thoroughly with the help of magnetic stirrer. The above procedure for chitosan was followed with carbopol 934p.

Table 1: Showing formulation design of formulations

S. No.	ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Thio colchicoside	500mg	500mg	500mg	500mg	500mg	500mg	500mg	500mg	500mg
2	Sodium alginate	500mg	600mg	700mg	800mg	500mg	600mg	700mg	800mg	800mg
3	Chitosan	5mg	10mg	15mg	20mg	-	-	-	-	10mg
4	CARBOPOL 934p	5mg	-	-	-	5mg	10mg	15mg	20mg	10mg
5	calcium chloride (%W/V)	10	10	10	10	10	10	10	10	10
6	Purified water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

The resulting bubble free dispersion was added manually drop wise with a 5 ml syringe (22 gauze needle) into 100ml of (10%w/v) calcium chloride solution ($cacl_2$) and stirred in a 250ml beaker. The gelation time of 15min was allowed to complete the curing reaction and produce spherical and rigid microspheres. The spheres so prepared were collected by decantation, washed with water and dried at 40^0c in hot air oven. The process was applied to 9 (i.e., F1-F9).different formulations by using varying proportions of chitosan, carbopol and sodium alginate**[9]**,as given in table no -1

Evaluation of Microspheres [10]

Particle size analysis

Size distribution of the microspheres was analyzed by scanning electron microscopy. Particle size distribution was measured by Dry Dispersion technique. Average particle size was expressed as volume mean diameter and surface weighted mean diameter in µm.

Entrapment efficiency

The drug entrapment efficiency of spheres was estimated by dispersing the spheres in 100 ml of phosphate buffer at 7.4 by vigorous shaking on mechanical shaker for 12 hr. Then, the solution was filtered, and the thiocolchicoside content was assayed by a UV spectro photometer at 353 nm.

The entrapment efficiency of micro spheres was calculated using the following formula.

$$\text{Entrapment efficiency} = \frac{\text{Estimated percentage drug loading} \times 100}{\text{Theoretical percentage drug loading}}$$

Swelling study

The swelling studies of spheres were performed in aqueous swelling media with pH 7.4 buffer at 37.5 ± 0.5^0C.The swelling ratio (Swt) was calculated from the following expression.

$$S\ wt = [(W_t - W_0) / W_0] \times 100$$

Where, W_t and W_0 are weight of sample Swollen at time 't' and weight of the original sample respectively.

Evaluation of mucoadhesive property

Apparatus used

Chicken intestine [11] (2x2cm), glass slides, USP tablet disintegration apparatus, phosphate buffer pH 7.4. Method The mucoadhesive property of microspheres was evaluated by an in vitro adhesion testing method known as wash off method. Freshly excised pieces of chicken intestinal mucous were mounted on to glass slides with cotton thread. About 20 microspheres were spread onto each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test, when the test apparatus was operated, the sample is subjected to slow up and down movement in the test fluid at 37^0C contained in a 1 liter vessel of the apparatus. At an interval of 30 min up to 8 hours the machine is stopped and number of spheres still adhering to mucosal surface was counted. The test was performed at intestinal (phosphate buffer pH 7.4) condition.

In vitro drug release study

The release of Thiocolchicoside from the microspheres was studied in phosphate buffer pH 7.4 as medium using dissolution test apparatus paddle type at 37.5^0C with a rotating speed of 50rpm.A sample of microspheres equivalent to 16 mg of thiocolchicoside was used in each test. At present time intervals 5ml aliquots were withdrawn and replaced by an equal volume of fresh dissolution medium. The samples were withdrawn through a membrane filter and were analyzed for thiocolchicoside content spectro photo metrically at 353nm using the UV-Visible Spectrophotometer.

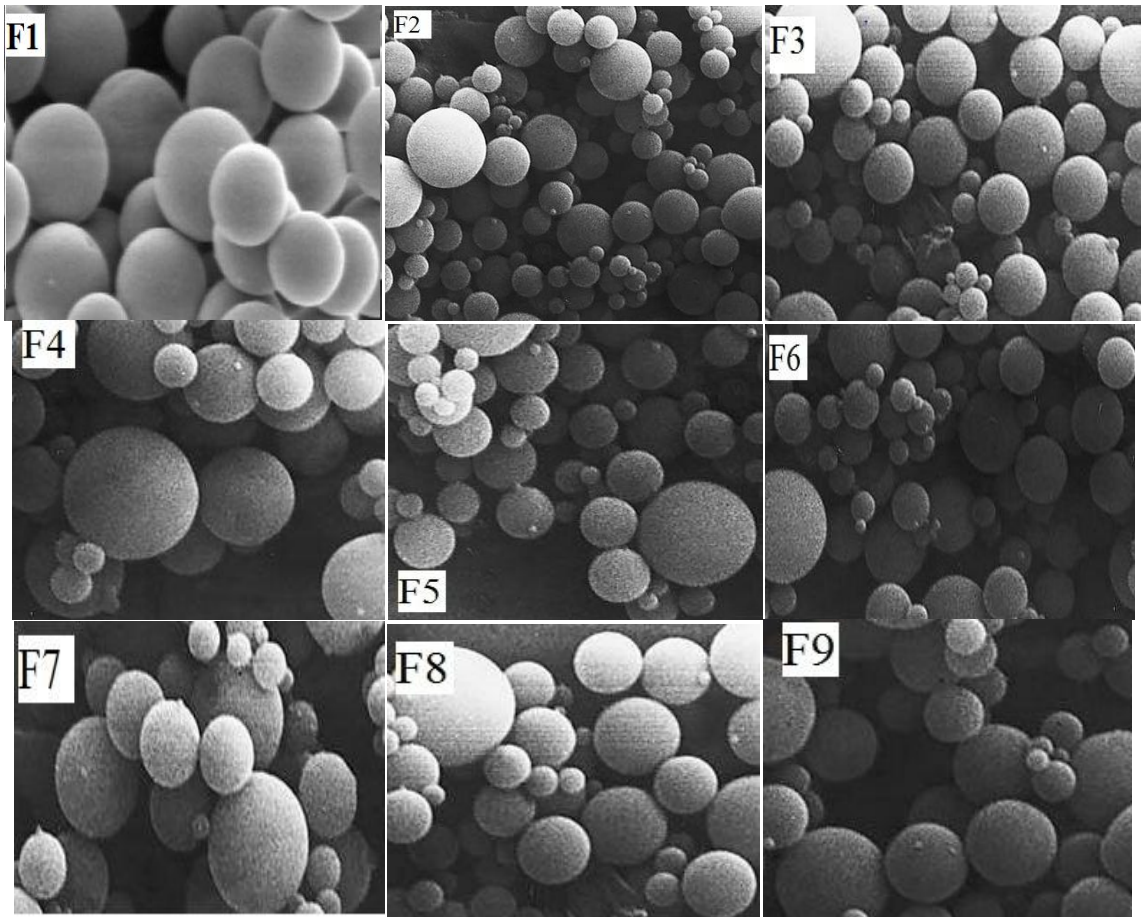

Fig. 1: Showing microspheres of all formulations

Table 2: Showing Entrapment Efficiency of all Formulations F1-F9

Formulation code	Weight taken (mg)	Media Qty (mL)	Entrapment efficiency
F1	25	50	52.55
F2	25	50	63.25
F3	25	50	76.55
F4	25	50	82.65
F5	25	50	58.56
F6	25	50	64.58
F7	25	50	79.65
F8	25	50	83.64
F9	25	50	92.55

Table 3: Showing swelling factor of all formulations F1-F9

Formulation	Initial weight(mg)	Final weight(mg)	Swelling factor (%)
F1	10	11.85	18.5
F2	10	13.85	38.5
F3	10	14.85	48.5
F4	10	16.15	61.5
F5	10	12.56	25.6
F6	10	14.55	45.5
F7	10	16.56	65.6
F8	10	17.65	76.5
F9	10	19.54	95.4

Table 4: Showing muco adhesion test data of all formulations F1-F9

Formulation	Initial	Final	% of adhesion
F1	20	6	30
F2	20	7	35
F3	20	9	45
F4	20	11	55
F5	20	6	30
F6	20	8	40
F7	20	11	55
F8	20	13	65
F9	20	16	80

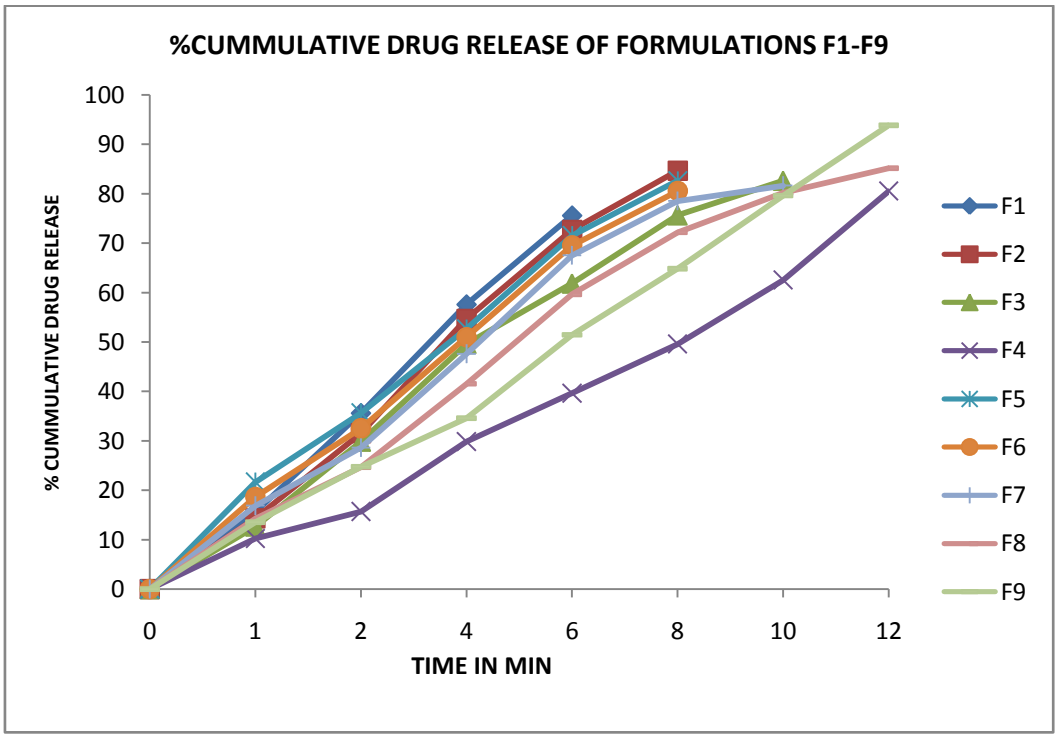

Fig. 2: Showing % cumulative drug release of formulations F1-F9

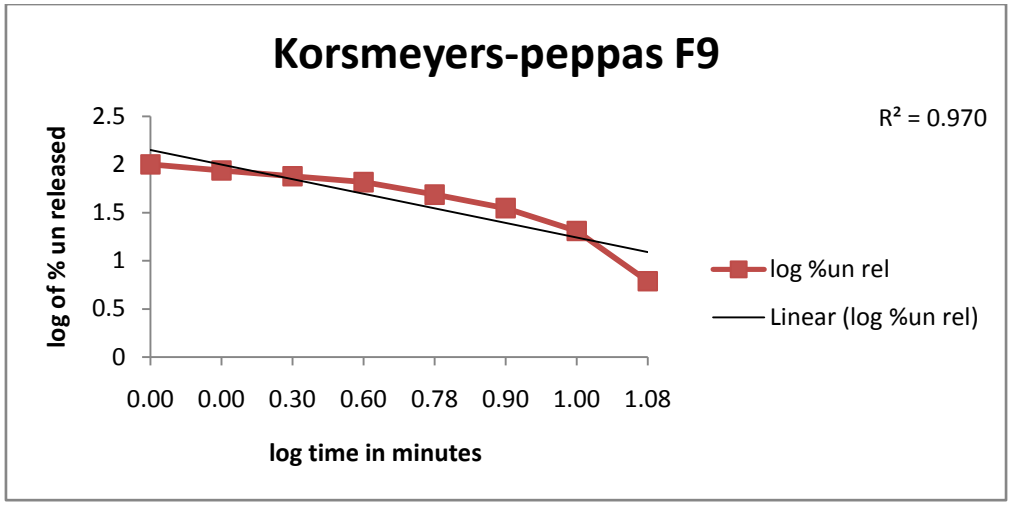

Fig. 3: Showing Korsmeyers-peppas plot of formulation F9

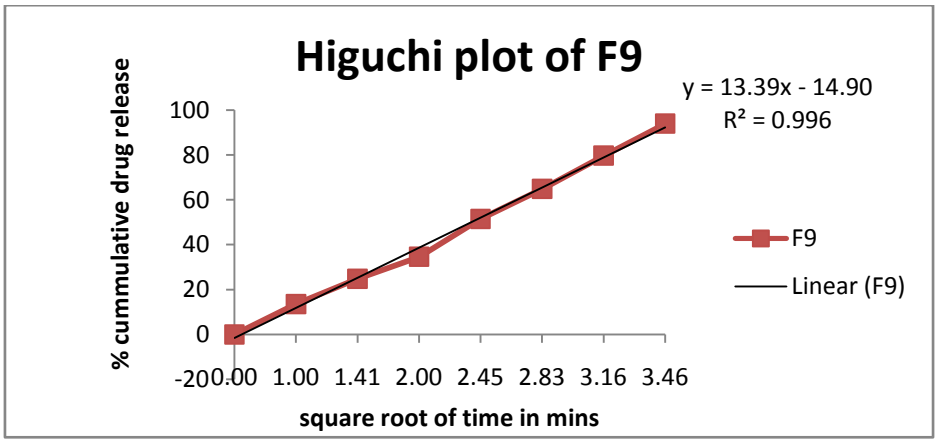

Fig. 4: Showing Higuchi plot of formulation F9

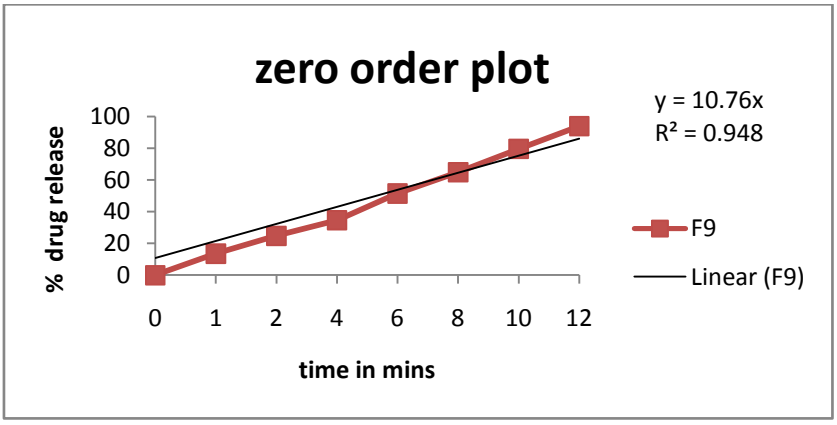

Fig. 5: Showing Zero order plot of formulation F9

Table 5: Showing mean diameter and surface weighted mean diameter in µm of all formulations F1-F9

Formulation	Mean population diameter µm (± SD)	SSA (m2/g X 10-2)b
F1	323±4.78	0.97
F2	352±2.58	1.25
F3	425±2.56	1.34
F4	521± 3.58	1.65
F5	315±3.56	0.79
F6	325±2.68	1.15
F7	398±2.97	1.39
F8	413±1.69	1.62
F9	375±1.27	1.79

RESULTS AND DISCUSSION

Particle size analysis

The effect of different parameters on particle size of micro spheres has been summarized in the table No.6. Increase in gel concentration increases the mean particle size of the spheres. This is due to the increase in viscosity, which in turn increase the droplet size.

Entrapment efficiency

The drug entrapment efficiency of different formulations has been summarized in the Table 2.The thiocolchicoside being soluble in water is having tendency to diffuse out to the aqueous medium. Due to addition of chitosan and carbopol934P good Entrapment efficiency was obtained due to hindered diffusion of the medicament through the gel barrier formed by the chitosan and carbopol. It was observed that, as the concentration of chitosan and carbopol increases, viscosity of resulting gel increases and thereby increases in entrapment efficiency.

Swelling study

Swelling ratio increases as the amount of polymer increases.

Mucoadhesion test

The adhesion of microspheres to the intestinal mucosa of chicken was evaluated as the mean percent of microspheres remain adhered after a defined period of washing .Results indicating that the mucoadhesive polymer to drug ratio had a significant effect on mucoadhesive property. The greater the concentration of the polymer associated with chitosan-alginate matrix and chitosan-carbopol matrix greater will be the adhesion.

In vitro drug release study

Data was plotted in figure :2 .Drug polymer ratios was found to affect the drug entrapment, particle size and ultimately the drug release characteristics of the prepared micro spheres .At higher polymer ratio the drug release from the micro spheres was slow as compared to lower polymer ratio. This was due to less particle of microspheres formed using low concentration of polymers .The release was only up to 6hrs. As the concentration of polymers increases along with chitosan/carbopol steady state release upto 10hrs was achieved and formulation F9 showed good reproducible results.

CONCLUSION

Thiocolchicoside mucoadhesive microspheres were prepared and evaluated. These were prepared using chitosan and carbopol as muco adhesive agents and sodium alginate as polymer. The formulation F9 was considered as best formulation since it showed good muco adhesive property and reproducible results in case of drug release studies.

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