ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2014; 5(2): 81 - 85

ORIGINAL RESEARCH ARTICLE

Formulation and Evaluation of the Wound Healing Chitosan Gel of Povidone Iodine

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Received 26 Dec 2013; Revised 01 Apr 2014; Accepted 11 Apr 2014

ABSTRACT

World demand for wound management products will increase 5.3 percent annually to $39.3 billion in 2016, serving a $9.3 trillion worldwide health care industry. This data not only emphasise on the economical growth but also on the need or formulation used for would management. The purpose of the Formulations which have been developed in this research work was to formulate chitosan based applicant having povidone iodine because of the wide use of chitosan as a wound healing agent and povidone iodine have been majorly used antiseptics. Several batches were formulated from GF1 to GF5 without drug and best batch was selected by determining pH, Viscosity, spreadibility, extrudability.The best batch from placebo batches further used to formulate drug entrapped batches from CG1 to CG4. These batches were evaluated for pH, Viscosity, spreadibility ,extrudability, drug entrapment and in-vitro drug release. Formulation code CG4 was selected as a best formulation because it revealed better in-vitro drug release acceptable viscosity.extrudability and spreadibility .

Key words: Applicant, Extrudability, Spreadability, Povidone iodine.

INTRODUCTION

"In recent years, accumulating knowledge regarding wound-healing process has led to the development of numerous therapies. World demand for wound management products will increase 5.3 percent annually to $39.3 billion in 2016, serving a $9.3 trillion worldwide health care industry. An expanding volume of surgical procedures coupled with a rising incidence of treated injuries and external skin conditions will underlie gains. Growth will also benefit from new product introductions, especially negative pressure therapy systems, skin replacements, tissue sealants, and wound healing agents. [1]

Wound healing is a complex process involving various mechanisms, such as coagulation, inflammation, matrix synthesis and deposition, angiogenesis, fibroplasia, epithelization, contraction and remodeling the fluids at wound sites may be an important reservoir of growth factors that promote the wound healing process. [2,3]

Chitosan is a polysaccharide comprising copolymers of glucosamine and N-acetyl glucosamine. It is derived by partial deacetylation of chitin from crustacean shells .Due to its high molecular weight of 50–2000 kDa, chitosan exhibits a positive charge and film-forming and gelation characteristics. Some research indicates that chitosan enhances the functions of inflammatory cells such as polymorphonuclear leukocytes, macrophages and fibroblasts; thus, it promotes granulation and organization. Therefore, chitosan can be used for large open wounds. Chitosan has desirable qualities, such as hemostasis, wound healing, bacteriostatic, biocompatibility, and biodegradability properties. [4,5]

Chitosan is reported for antiseptic, antibacterial and wound healing .Chitosan gel also acts as an ideal wound dressing. It is biocompatible, biodegradable, hemostatic, anti-infective and, more importantly, it accelerates wound healing. Chitosan gel has a strong tissue-adhesive property. A previous study showed that chitosan-treated wounds were epithelized prior than wounds of the control group after the treatment. [6]

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It was also observed that chitosan solution in acetic acid give more irritation than lactic acid and that was the reason why lactic acid was selected as a solvent for chitosan in present research work. 7Povidone iodine is used as antiseptic, as it is broad spectrum antiseptic for topical application in the treatment and prevention of infection in wounds. In the present work attempt has been made to prepare povidone iodine gel as a wound healing formulation.

MATERIALS AND METHODS

Chitosan (deacetylation degree of 75–85% and MW w190, 000–310,000) was obtained from Central institute of Fisheries technology, Cochin. All other materials were obtained from Central Drug Ltd (Delhi).

Preparation of Chitosan gel:

Chitosan gels were prepared by incorporating different concentration (2%,2.5%,3%,3.5%, and 4%) w/v of chitosan in 1% (v/v) lactic acid solution in deionized water . For preparation of 2%w/v chitosan gel weighed amount of chitosan was taken and added slowly in to 1% v/v lactic acid solution with constant stirring on magnetic stirrer. After the stirring of two h chitosan gel was subjected for two cycles of sonication fot 480 seconds to expel out the entrapped air bubbles from the prepared gel and then it was filled in the wide mouth glass bottle of 100 ml. Similarly other gel formulation were prepared but since they had different viscosity hence intermittent sonication cycles of 10 minutes to 32 minutes are required for expulsion of entrapped air bubble (**Table 1**).

pH measurement:

pH determination of prepared formulations was done by using pH meter . The procedure was carried out by taking gel in 250 ml beaker immersing pH electrode into the formulation and readings of pH meter were recorded. Same process was repeated two more time with the same formulation. Similar procedure was used for the determination of the pH of all the prepared formulation thrice and results are mentioned in (**Table 2**).

Viscosity Determination -

The measurement of viscosity of different formulation was done by using Brookfield viscometer having T shape LV spindle .The procedure used was pouring gel into the beaker of 250 ml and fixing temperature probe to the wall of beaker by frame clip and the temperature was recorded, rotation speed of spindle was set at 30 rpm and viscosity was recorded. After that rotation speed was further set to 50 rpm and viscosity was recorded. Viscosity of all the prepared formulations and marketed gel Diclogel were recorded using same method (Table 2).

Spreadability:

The procedure used for measurment of spreadability of prepared gel formulation was done by using 'Spreadability Apparatus'. A Wooden rectangular block was prepared and on to one end of rectangular block a glass slide was fixed, and one another movable glass slide (5x2cm) was kept over the lower fixed glass slide and it was attached by a string running on a pulley whose other end was hanging downward.

The hanging end of the string attached with the 50 g weight, which helps determining the spreadability of prepared formulation. The process was carried out by pouring 1gm of gel on the fixed glass slide and movable glass slide was kept over it which is attached with 50 g of weight via string, time taken by the upper slide to reach other end 7.6 cm away from the initial point in length was measured, Then spreadability was determined by using formula:

S= MxL/T

Where, M = weight tide 50 g with upper slide,L = length moved on the glass slide and T = time taken.

Similar procedures were followed for all the prepared formulations and Diclogel and results are mentioned in (**Table 3**).

Extrudability

The method was carried out by fixing sealed side of formulated gel filled collapsible tube having dimension 5x2cm ,capacity holding 10g , laid down horizontally on scaled glass plate ,pressure was applied on the sealed end of the collapsible tube by increasing the weight on the disc 2 cm diameter designed to apply weight on the sealed end of the tube. The weight in grams required to extrude 0.5 cm of gel on scaled glass plate was measured (**Table 3**). [3]

The optimized formulation was selected by comparing the prepared formulation with the marketed formulation of Diclogel, It was observed that pH and viscosity of the prepared formulation GF4 containing 3.5 %w/v concentration of chitosan in 1% v/v lactic acid solution, is quite similar to the pH and viscosity of the marketed formulation and revealed shear thinning property of the Chitosan gel as compared to the other

formulation prepared showed viscosity less than 4900 mPas.

Other evaluation parameters such as spreadability and extrudability were also studied and revealed almost similar results of marketed formulation and formulation code GF4 as compare to the other formulation prepared. Hence it could be conclude from the results obtained that formulation code GF4 acts as excellent gel in 3.5 %w/v concentration of chitosan.

After observing the mentioned properties the best suited optimized formulation was found to be GF4 which was further formulated by entrapping povidone iodine in different concentration as mentioned in the (**Table 4**).

Percent Drug Entrapment:

The best batch GF4 which was found to be good in all the evaluation parameters was further optimized by entrapping drug in increasing concentration.

The percent drug entrapment study was carried out by taking 1 g of gel and suspending it in 50 ml of phosphate buffer 7.4 pH .The mixture was stirred 2 hours vigorously and the content was filtered finally iodine concentration was evaluated by iodometric titration.The drug concentration that has been added to form CG1, CG2, CG3 and CG4 were 9%, 10%11% and 12%w/w respectively to enhance drug entrapment efficiency (**Table 7**).

***In vitro* Percent Drug release**:

Different prepared formulation of gel were analyzed for in vitro drug release .One gram of prepared formulation applied on the glass slide which was immersed in to modified diffusion cell apparatus containing phosphate buffer pH 7.4 at 37± 0.5ºC temperature. The solution was gently stirred at 28rpm and after every hour up to 10 hours aliquot was withdrawn and the amount of drug released from the gel was determined by Iodometric titration using sodium thiosulphate as a titrant and starch solution as an indicator In order to keep the volume constant, same amount of fresh buffer solution was replaced after each sampling.

RESULTS

The gel containing higher concentration of polymer is opaque in nature while gel having lower concentration of polymer was translucent in nature.

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Firmulation GF4 was further formulated by entrapping povidone iodine in different 9%, 10%, 11% and 12%w/w concentration as mentioned in the (**Table 4**).

The drug entrapped gel so formulated were further evaluated for pH, viscosity ,spreadability , extrudability , entrapment efficiency and in-vitro drug release as shown in (**Table 5,6 & & 7**).

Drug entrapment study were also performed and it was observed that formulation CG4 showed maximum drug entrapment efficiency 1.15% , because of the same obvious reason that formulation containing higher drug concentration showed high entrapment efficiency as mentioned above formulation CG4 containing 1.44% of drug which contained maximum concentration of drug among all the drug entrapped gel formulation prepared .

In vitro percent drug release also revealed similar result which was found to be maximum 69.5% in the formulation CG4 having highest concentration of the drug. The above mentioned results indicates that formulation CG4 is the final optimized gel formulation of the chitosan and this could be further subjected for the in vivo wound healing activity (**Figure 1**).

Table 1: Different formulations of Chitosan gel without drug

S. No	Formulation code	Chitosan w/v %	Lactic acid v/v %
1	GF1	2	1
2	GF2	2.5	1
3	GF3	3	1
4	GF4	3.5	1
5	GF5	4	1

Showing different formulations of chitosan having different concentration of chitosan

Table 2:pH and viscosity of different drug entrapped formulations at 30 and 50 rpm

Formulation code	At 30rpm (mPas)	At 50rpm (mPas)	pH
GF1	20.3 ± 0.5	16 ± 0.6	5.2±0.1
GF2	455 ±0.7	279 ±0.6	5.6±0.3
GF3	1068 ± 1	576.3 ± 2	5.6±0.3
GF4	6319 ± 3	3341 ± 3	5.9±0.1
GF5	N F	N F	5.7±0.1
Diclogel	4900± 0.5	987± 0.8	6±0.1

It shows pH and viscosity of drug free gel at 30rpm and 50rpm

Table 3: Spreadability and Extrudability of chitosan formulation without drug

Formulation code	Spreadability(g cm / s)	Extrudability(g)
GF1	34.5	600 ±3
GF2	21.1	705 ±2
GF3	13.5	720 ±2
GF4	9.5	1000 ± 3
Diclogel	9.9	907 ± 0.2

Showing spreadability and extrudability of drug free chitosan gel and its comparison with market formulation Diclogel

Table 4: Povidone iodine entrapped drug formulation

S. No	Formulation codes	% Drug added in formulations
1	CG 1	1.08%
2	CG 2	1.20%
3	CG 3	1.32%
4	CG 4	1.44%

Showing percentage of Povidone iodine added in the drug entrapped chitosan gel

Table 5: Viscosity and pH of drug entrapped wound healing gels

Formulation code	pH	At 30rpm(mPas)	At 50rpm (mPas)
CG 1	5.9 ± 0.1	6489±38	3482±27
CG 2	5.9 ±0.3	6689±32	3762±17
CG 3	5.9 ±0.7	6989± 40	3880±63
CG 4	6±0.1	7319± 34	4132±43

Showing pH and viscosity of drug entrapped gel at 30rpm and 50rpm

Table 6: Spreadability and extrudability of drug entrapped different gel formulations

Formulation code	Spreadability (g cm / s)	Extrudability Weight in (g)
CG 1	10	1000 ± 57
CG 2	10.1	1050 ± 76
CG 3	10.5	1070± 84
CG 4	10.9	1090 ± 60

Showing Spreadability &extrudability of drug entrapped chitosan gel formulations

Table 7: Entrapment efficiency of different drug entrapped formulations

S. No	Formulation codes	(%) Drug entrapped
1	CG 1	0.8%
2	CG 2	0.9%
3	CG 3	1.07%
4	CG 4	1.15%

Showing percentage drug entrapment of different drug entrapped gels

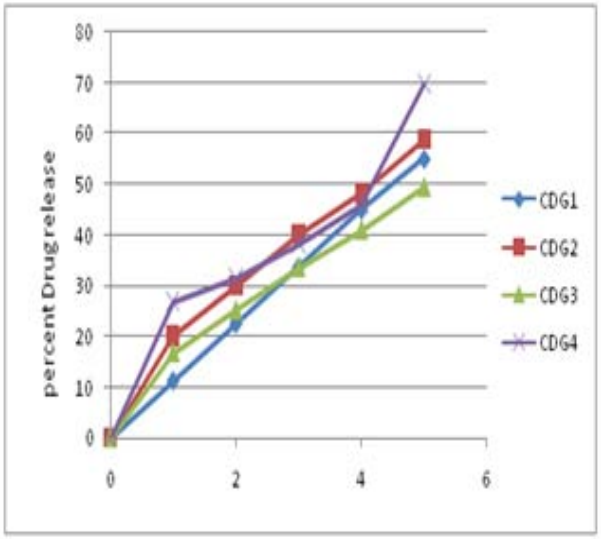

Fig 1: Here CDG1 to CDG4 are *In vitro* percent drug release of different formulations from CG1 To CG4

CONCLUSION

For *in-vivo* wound healing activity, the same formulation CG4, which has proved to be the best for *in-vitro* release rate profile, was selected. Hence it can be concluded that formulation CG4 is a promising wound healing formulation.

ACKNOWLEDGEMENTS

I am thankful to Dr A.K Pathak Head of Department of Pharmacy Barkatullah University to provide research facility. I am also thankful of Dr Subhas Pande Sr Vice President Corporate – Quality Assurance, Cadila Health Care Limited , Ahmedabad for his constant support.

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