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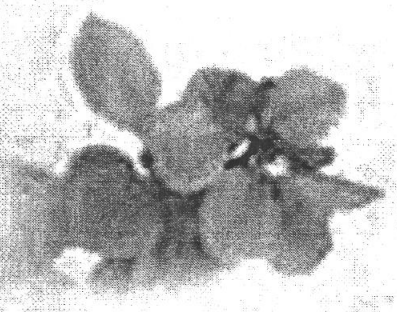

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Enhanced production of butyric acid by solid-state fermentation of rice polishings by a mutant strain of Clostridium tyrobutyricum HTML (abstract.php?id=2184&aTitle=Enhanced production of butyric acid by solid-state fermentation of rice polishings by a mutant strain of Clostridium tyrobutyricum) | Fulltext (../admin/12389900798187/2018_17_7_2.pdf)

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Suppression of long non-coding RNA H19 inhibits proliferation, cell migration and invasion in human cervical cancer cells HTML (abstract.php?id=2186&aTitle=Suppression of long non-coding RNA H19 inhibits proliferation, cell migration and invasion in

human cervical cancer cells) | Fulltext (../admin/12389900798187/2018_17_7_4.pdf)

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Peptide 17, an inhibitor of YAP/TEAD4 pathway, mitigates lung cancer malignancy HTML (abstract.php?id=2187&aTitle=Peptide 17, an inhibitor of YAP/TEAD4 pathway, mitigates lung cancer malignancy) | Fulltext (../admin/12389900798187/2018_17_7_5.pdf)

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Characteristics and anticancer properties of Sunitinib malate-loaded poly-lactic-co-glycolic acid nanoparticles against human colon cancer HT-29 cells lines HTML (abstract.php?id=2188&aTitle=Characteristics and anticancer properties of Sunitinib malate-loaded poly-lactic-co-glycolic acid nanoparticles against human colon cancer HT-29 cells lines) | Fulltext (../admin/12389900798187/2018_17_7_6.pdf)

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http://dx.doi.org/10.4314/tjpr.v17i7.6 (http://dx.doi.org/10.4314/tjpr.v17i7.6)

Apoptosis-inducing effect of 6,7-dimethoxy-4-hydroxy-8-formylflavon from Nicotiana tabacum L leaf in human hepatoma HepG2 cells via activation of mitochondria-mediated apoptotic pathway HTML (abstract.php?id=2189&aTitle=Apoptosis-inducing effect of 6,7-dimethoxy-4-hydroxy-8-formylflavon from Nicotiana tabacum L leaf in human hepatoma HepG2 cells via activation of mitochondria-mediated apoptotic pathway) | Fulltext (../admin/12389900798187/2018_17_7_7.pdf)

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Huma Aslam, Arif-ullah Khan (mailto:arif.ullah@riphah.edu.pk), *Humaira Naureen, Fawad Ali, Farhat Ullah, Abdul Sadiq,*

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Honey, Fertility, Spermatozo (Honey, Fertility, Spermatozo)

Antitumor effects of candidone extracted from Derris indica (Lamk) Bennet in cholangiocarcinoma cells HTML (abstract.php?id=2198&aTitle=Antitumor effects of candidone extracted from Derris indica (Lamk) Bennet in cholangiocarcinoma cells) | Fulltext (../admin/12389900798187/2018_17_7_16.pdf)

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Indonesian Pasuruan propolis extract does not exert anti-proliferation and pro-apoptotic effect on human colon carcinoma cell line HT-29 HTML (abstract.php?id=2199&aTitle=Indonesian Pasuruan propolis extract does not exert anti-proliferation and pro-apoptotic effect on human colon carcinoma cell line HT-29) | Fulltext (../admin/12389900798187/2018_17_7_17.pdf)

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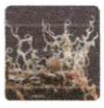

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Effect of hydroalcohol extract of lemon (Citrus limon) peel on a rat model of type 2 diabetes HTML (abstract.php?id=2202&aTitle=Effect of hydroalcohol extract of lemon (Citrus limon) peel on a rat model of type 2 diabetes) | Fulltext

(../admin/12389900798187/2018_17_7_20.pdf)
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http://dx.doi.org/10.4314/tjpr.v17i7.20
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Anti-diabetic activity of aqueous extract of Fructus Ligustri Lucidi in a rat model of type 2 diabetes HTML (abstract.php?id=2203&aTitle=Anti-diabetic activity of aqueous extract of Fructus Ligustri Lucidi in a rat model of type 2 diabetes) | Fulltext (../admin/12389900798187/2018_17_7_21.pdf)
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Investigation of nedaplatin and CpG oligodeoxynucleotide combination therapy in a mouse model of lung cancer HTML (abstract.php?id=2204&aTitle=Investigation of nedaplatin and CpG oligodeoxynucleotide combination therapy in a mouse model of lung cancer) | Fulltext (../admin/12389900798187/2018_17_7_22.pdf)
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http://dx.doi.org/10.4314/tjpr.v17i7.22
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Inhibitory effect of α-cyclodextrin on α-amylase activity HTML (abstract.php?id=2205&aTitle=Inhibitory effect of α-cyclodextrin on α-amylase activity) | Fulltext (../admin/12389900798187/2018_17_7_23.pdf)
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Urinary paraquat concentration and white blood cell count as prognostic factors in paraquat poisoning HTML (abstract.php?id=2206&aTitle=Urinary paraquat concentration and white blood cell count as prognostic factors in paraquat poisoning) | Fulltext (../admin/12389900798187/2018_17_7_24.pdf)
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Synthesis of 3-[4-(2-furoyl)-1-piperazinyl]-N-(substituted)propanamides as promising antibacterial agents with mild cytotoxicity HTML (abstract.php?id=2207&aTitle=Synthesis of 3-[4-(2-furoyl)-1-piperazinyl]-N-(substituted)propanamides as promising antibacterial agents with mild cytotoxicity) | Fulltext (../admin/12389900798187/2018_17_7_25.pdf)
Ghulam Hussain, Muhammad A Abbasi (mailto:abbasi@gcu.edu.pk), *Aziz-ur-Rehman , Sabahat Z Siddiqui, Irshad Ahmad, Rabia Malik, Muhammad Shahid, Zahid Mushtaq, Syed AA Shah,*
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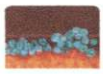

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effect of tigecycline HTML (abstract.php?id=2208&aTitle=Etiologic analysis of Chinese patients with agranulocytosis and hematopathies infected with resistant bacteria: Anti-bacterial effect of tigecycline) | Fulltext (../admin/12389900798187/2018_17_7_26.pdf)

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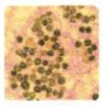

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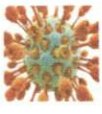

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Review Article

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Original Research Article

Influence of drug-polymer ratio on physical characteristics and release of metformin hydrochloride from metformin-alginate microspheres

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Abstract

Purpose: *To investigate the effect of drug and polymer ratio on the physical characteristics and release rate of metformin hydrochloride from alginate microspheres.*
Methods: *Microspheres were prepared by ionotropic gelation aerosolization technique using sodium alginate as polymer and calcium chloride as crosslinker. Three formulations of drug and alginate polymer ratios: 1:1 (F1); 1:1.5 (F2); and 1:2 (F3), and 10 % calcium chloride ($CaCl_2$) were investigated. The microspheres were studied with respect to physical characteristics, release profile and release rate. Release evaluation was done at pH 1.2 in hydrochloric acid (HCl) for 2 h, and in phosphate-buffered saline (PBS) at pH 7.4 for 12 h.*
Results: *Drug loading in formulations F1, F2 and F3 were 3.08 ± 0.21, 3.34 ± 0.28, and 3.99 ± 0.19 %, respectively. Low entrapment of below 15 % was achieved for all formulations, whereas high yield (above 45 %) was obtained. Drug release above 74 % was observed for all formulations. The release rates of F1, F2 and F3 were 9.6390 x 10-2, 9.0985 x 10^{-2}, and 8.3312 x 10^{-2} %/min, respectively.*
Conclusion: *Metformin-alginate microspheres can be used for optimized formulations with good physical characteristics and in vitro release. These findings suggest that the microspheres might be a potent drug delivery system for the treatment of diabetic mellitus.*

Keywords: *Metformin, Alginate microspheres, Drug-polymer ratio, Aerosolization, Drug release*

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INTRODUCTION

Diabetes is a chronic metabolic disease characterized by high fasting blood sugar levels [1]. Metformin hydrochloride (metformin HCl) is a biguanide drug used for treating non-insulin dependent diabetes mellitus [2,3]. However, metformin HCl has a short half-life of about 2.7 to 4 h, thereby necessitating frequent administration to patients for control of blood glucose [4,5]. One way of solving this problem is by encapsulating the drug in the microsphere delivery system to prolong its half-life and minimize its side effects [6].

Microspheres are drug-containing matrix systems with sizes in the range 5 - 5000 µm, and are usually used for slow and controlled-release [7,8]. Ionotropic gelation is a simple, quick and cost-effective method which is able to crosslink to counter ions to form hydrogel using drop or aerosolization [9,10]. Alginate is an anionic, biocompatible and biodegradable polysaccharide comprising L-glucuronic (G) and D-mannuronic acid (M) subunits [11-14]. Alginate forms egg-box gels with a divalent cation such as Ca^{2+} [13]. Microsphere formulations are influenced by factors such as drug, polymer and cross-linker concentrations; cross-link time and ratio of drug to polymer [15]. Some studies used polymer : drug ratios of 1:1, 1:1.5 and 1:2 to improve the entrapment efficiency of metformin HCL from 66.7 to 85.08 % [13,16,17]. However, the size of the microspheres produced was still large (100 - 480 µm). Therefore, there is need for optimal polymer and drug concentrations [18]. To improve their stability, microspheres have been formulated in dry forms using freeze drying and maltodextrin as lyoprotectant [19,20]. The aim of the present study was to investigate the effect of drug : polymer ratios on the physical characteristics and release of metformin HCl from alginate microspheres.

EXPERIMENTAL

Materials

Metformin HCl was product of Combiphar; sodium alginate was obtained from Sigma-Aldrich Inc.; while food grade $CaCl_2H_2O$, sodium citrate, maltodextrin and aquadest were products of PT.Bratachem. Hydrochloric acid, Na_2HPO_4, KH_2PO_4, phosphate buffered saline (PBS), NaOH and NaCl were supplied by Merck). Metformin, sodium alginate and citrate were pharmaceutical grade.

Formulation of microspheres

The production of metformin HCl-alginate microspheres using aerosolization technique was started by dissolving Na Alginate in 100 ml distilled water to yield 0.5, 0.75 and 1.0 % solutions. Metformin HCl (500 mg) was then dispersed into the resultant alginate solutions, and mixed until homogeneous. A solution of $CaCl_2$ was made in 100 mL of aquadest according to the concentration in the formula. Each dispersed solution of metformin HCl-alginate was sprayed into the $CaCl_2$ solution using a spray aerosol of aperture 35 µm at a constant pressure of 40 psi. The distance between the atomizer and the surface of the $CaCl_2$ solution was maintained at 8 cm, and the sprayed mixture was stirred with a magnetic stirrer for 30 min at 1000 rpm. The resultant microspheres were separated from the $CaCl_2$ by centrifugation at 2500 rpm for 6 min, washed twice with aquadest, and suspended in 5 % maltodextrin lyoprotectant. Finally, the microspheres were freeze-dried at - 80 °C for 29 h. The compositions of the various microspheres are shown in Table 1.

Table 1: Compositions of metformin HCl-alginate microspheres

Ingredient	Function	F1	F2	F3
		1:1	1:1.5	1:2
Metformin HCl (mg)	Active agent	500	500	500
Na Alginate (mg)	Polymer	500	750	1000
$CaCl_2$ (%)	Crosslinker	10	10	10
Crosslinking time (min)	-	30	30	30
Maltodextrin (%)	Lyoprotectant	5	5	5

Formulation F1: Metformin HCl-alginate microspheres with drug: polymer ratio 1:1
Formulation F2: Metformin HCl-alginate microspheres with drug: polymer ratio 1:1.5
Formulation F3: Metformin HCl-alginate microspheres with drug: polymer ratio 1:2

Evaluation of entrapment efficiency and drug loading

Microspheres (150 mg) were added to 50 ml of 0.5 M Na Citrate buffer, pH 8.5. The mixture of microspheres and Na Citrate was stirred using a magnetic stirrer at 1000 rpm for 3 h, and the absorbance of the sample solution was read in a spectrophotometer at 239 nm. The entrapment efficiency was calculated from the content of metformin HCl in microspheres as the ratio of metformin HCl to theoretical content of metformin HCl expressed as a percentage, while drug loading was computed as the ratio of the weight of the dry microspheres to the weight of the initial microspheres expressed as a percentage.

Determination of yield

The yield of microspheres was calculated as the ratio of the dry microsphere to the total weight of the ingredients used in producing the dry microspheres.

Morphological examination

The morphology of the metformin HCl-Alginate microspheres were evaluated using an optical microscope, while that of the dry microspheres

was observed with a scanning electron microscope (SEM).

In vitro drug release studies

In vitro drug release studies were conducted by first constructing a standard curve of metformin HCl in HCl at pH 1.2, and in PBS at pH 7.4. Metformin HCl release from microspheres was studied in a thermoshaker at 37 °C at a speed of 100 rpm. Each formulation of microspheres weighed 750 mg. This was added to the release medium. The release medium (100 ml of HCl, pH 1.2) was prepared and thermostated at 37 ± 0.5 °C. Once the temperature reached 37 ± 0.5 °C and speed was set up at 100 rpm, samples of the HCl medium, pH 1.2 were removed at the rate of 3.0 ml/min at 10, 30, 60, and 120 min. Each withdrawn sample was replaced with an equivalent volume of the release medium at the same temperature. Then, the pH of the medium was adjusted to 7.4 by adding 10.597 grams Na_2HPO_4; $2PO_4$ 1.499 gram, and 2.4 ml of 3 N NaOH. Thereafter, samples were withdrawn from the new release medium of pH 7.4 at 130, 180, 240, 360, 480, 600 and 720 min. the samples taken were replaced with phosphate buffered saline (PBS) pH 7.4 ± 0.05 at the same temperature. The samples were filtered through a filter paper (0.45 µm pore), and their absorbance was read at 232 nm in a spectrophotometer. The Metformin HCl concentrations were obtained from the standard curve regression equation of metformin HCl solution at 232 nm

Statistical analysis

Drug loading, entrapment efficiency and yield were analyzed statistically using one way analysis of variance (ANOVA) with IBM SPSS Statistic 22.0 program at 95 % confidence level.

RESULTS

Optical microscopy of the morphology of the wet microspheres F1, F2 and F3 showed spherical shape and smooth surfaces. The addition of maltodextrin lyoprotectant resulted in microspheres with a spherical shape and a smooth surface. This was also evident from the results of SEM on the dry microspheres (Figure 1).

Data on drug loadings of metformin HCl in microspheres, entrapment efficiency and yield are presented in Table 2. The flux of metformin HCl from microspheres, and their release profiles at pH 1.2 and pH 7.4 are shown in Table 3 and Figure 2, respectively.

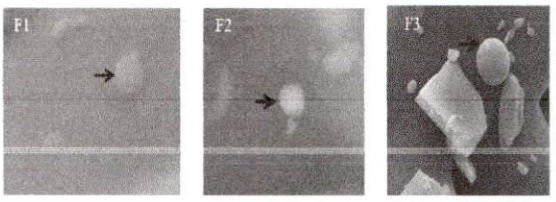

Figure 1: Morphologies of dry microspheres as seen using SEM

Table 2: Entrapment efficiency, drug loading and yield in the microsphere formulations

Formulation	Metformin loading	Entrapment efficiency	Yield
F1	3.08 ± 0.21	6.70 ± 0.20	47.69 ± 6.33
F2	3.34 ± 0.28	9.66 ± 0.42	58.91 ± 3.30
F3	3.99 ± 0.19	13.63 ± 0.21	65.46 ± 5.72

Table 3: Release rate (flux) of metformin HCl from the microspheres

Formulation	Mean slope ± SD
F1	$9.6390 \times 10^{-2} \pm 0.9077 \times 10^{-2}$
F2	$9.0985 \times 10^{-2} \pm 3.1949 \times 10^{-2}$
F3	$8.3312 \times 10^{-2} \pm 2.0656 \times 10^{-2}$

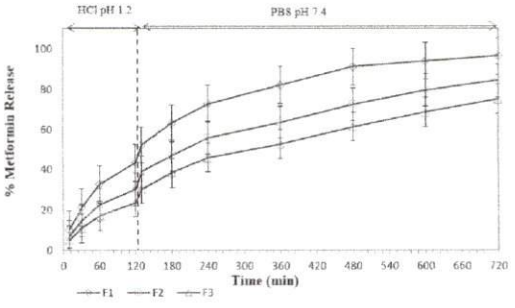

Figure 2: Release profiles of metformin HCl from the microspheres in solution pH 1.2 and 7.4

DISCUSSION

In this study, the addition of maltodextrin resulted in the spherical shape and smooth surface of the microspheres. This was due the covering of cavities or pores on the surface of the microspheres, thus increasing their number and size through the formation of hydrogen bonds with polar groups on the surface of microspheres [20]. The amorphous form of maltodextrin maximized the number of hydrogen bonds formed [20,22]. The particle size of microspheres was about 3 µm in the three formulations.

Results of loadings, entrapment efficiency and yield showed that metformin HCl loading in microspheres increased in response to increases in alginate polymer levels. This was so because increased levels of alginate enhanced the degree of cross-links, thereby increasing the availability of calcium binding sites in the polymer chain, and hence the capacity of the microspheres to bind the drug [21,23]. In addition, increases in polymer: drug ratios enhanced entrapment efficiency because an increase in polymer increases the encapsulation of metformin HCl [25]. Thus, the entrapment efficiency of F3 was greater than that of F2 or F1.

The yield of the three formulations suggested that increased polymer concentration enhanced microsphere yield. Following evaluations of drug loadings and entrapment efficiency, further experiments on release testing was conducted. The release rate study was performed in two phases because the release was made to mimic physiological conditions. In the first phase, microspheres were incubated in HCl at pH 1.2 for 120 min. Conditions in this first phase resembled those of the stomach, where gastric pH during fasting reaches 1 – 2, with gastric emptying time of about 2 - 6 h, depending on the amount and type of food consumed. After sampling for 120 min, the pH of the HCl medium was adjusted to 7.4 ± 0.5, to mimic the pH of the intestine, and used to evaluate metformin HCl release at alkaline pH. The cumulative percentage release of metformin HCl for 12 h from F1, F2 and F3 were 96.40 ± 7.37, 84.27 ± 13.96, and 74.98 ± 12.95 %, respectively.

Based on results obtained from release profile were in accordance with the hypothesis at the outset that amount of metformin hydrochloride were separated at acidic pH and amount of drug were loose at alkaline pH was greater and constantly released within certain time.

It has been reported that an increase in polymer concentration increased the entrapment capacity of drugs in microspheres [21]. Increasing concentrations of alginate microspheres will lead to slower release because the surface of microspheres becomes coated with polymer, leading to slower diffusion of drug out of the matrix [25]. The rate of release was obtained by regression at steady state conditions. The slope of the regression equation showed the rate of release (flux) of metformin HCl from the alginate microspheres. The flux of F1, F2 and F3 were 9.6390×10^{-2}, 9.0985×10^{-2}, and 8.3312×10^{-2} %/min, respectively. These results indicated a trend in which increased concentrations of alginate decreased the release rate of metformin HCl. When the concentration of alginate is increased, the thickness of the layer around drug particles is also increased [21]. A decrease in the release rate of a drug may occur as a result a decrease in the diffusion coefficient of the drug, the pore size of particles and the rate of particle swelling in body fluids so that the penetration rate of body fluids into the particle decreases [21,25]. Statistically significant differences were seen in the metformin HCl release rates of F1, F2 and F3. This may be caused a number of factors: the concentration of the polymer used was probably not enough for optimal crosslinker levels. Moreover, it is possible that the crosslinking time, and the stirring speed were not optimal. Metformin HCl-alginate microsphere preparation by ionotropic gelation method at drug : polymer ratios of 1: 1; 1: 1.5; and 1: 2 did not provide significant differences in the release rates. Thus, further research to improve drug loadings and *in vivo* tests were needed.

CONCLUSION

This research has formulated optimized metformin-alginate microspheres and showed their good physical characteristics and *in vitro* drug release profiles. These findings suggest that the microspheres might be potent drug delivery systems for the treatment of diabetic mellitus.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Author contribution

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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