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Sustained Delivery of Pentazocine from Mucoadehsive Buccal Patches to Improve Anti-Addiction Therapy During COVID-19 Pandemic

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Abstract

Introduction: Both, COVID-19 and addiction have formed the dangerous duo which fueled each other's propagation. During this period of disastrous pandemic, all the nations should address the various issues of the addicts with the utmost care. 2019-coronavirus disease (COVID-19) is causing insurmountable psychosocial impact on the whole mankind. This article deals with the sustained delivery of pentazocine from mucoadehsive buccal patches to improve anti-addiction therapy. It is a small piece contribution of polymer chemists for the addicts during COVID-19. Recently, it has been found that drugs used during addiction therapy turn out to be addictive in nature when used in higher concentration for longer time. These drugs start acting as abused substances that are the major point of concern in the present work. Hence, some controlled and sustained drug delivery systems were required for the delivery of these compounds. Polysaccharide can act as potential candidate for the developing the formulations for the same.

Methods: Pentazocine is an opioid analgesic that has mixed opioid agonist and antagonist actions. The controlled release pentazocine loaded pectin-psyllium poly (acrylic acid) based formulations were prepared by copolymerization method. In vitro release profile of the drug was determined along with the evaluation of biomedical properties.

Results: The calibration curves of pentazocine lactate were prepared at λmax 277 nm on UV-Visible Spectrophotometer. The loading of the drug was found 42%. The values of the diffusion exponent 'n' were found 0.60.

Conclusions: The release of pentazocine (a model anti-addiction compound) from polymer matrix occurred slowly in controlled manner without any burst effect and followed Non-Fickian type diffusion mechanism. The polymer samples were haemocompatible, mucoadhesive and antioxidant and could be utilized as buccal patches to improve anti-addiction therapy. This will overcome the draw backs associated with the conventional formulations of the anti-addiction drugs. Overall, controlled and sustained delivery of anti-addiction drugs from drug loaded drug delivery systems could exert of various benefits especially in case of drugs like pentazocine to improve anti-addiction therapy during COVID-19 pandemic. Overall the present work is an attempt to design the drug delivery carrier for the sustained delivery of pentazocine from buccal patches to improve anti-addiction therapy during COVID-19 pandemic

INTRODUCTION

Addiction in general is consider as a disease of isolation and addiction substance users can be returned to a drug-free life through medication beside other actions including family support, socialization, cognitive and behavioral therapy [1]. At the same time, 2019-coronavirus disease (COVID-19) has left harmful psychosocial impact on the whole mankind and it is matter of great concern that addicts have been extremely badly affected by the COVID-19 crisis [2]. Both, COVID-19 and addiction have formed the dangerous duo which fueled each other's propagation. During this period of disastrous pandemic, all the nations should address the various issues of the addicts with the utmost care [3]. Recently, Dubey and coworkers [4]. have evaluated the bi-directional relationship between COVID-19 and addiction and found that both problems are at the verge of collision will cause major health hazard and it was recommended that prescribed de-addiction drugs should be easy accessible. Burt at the same time, those who take opioid for therapy are at risk of fatal over-dosage which is responsible for various complications and worsen outcome of COVID-19 [5]. Here the

slow and sustained release of drugs like buprenorphine has provided proven treatment of medication and better patients compliance has been achieved [6]. Vecchio and coworkers [7] have concluded in their research report that easy access to prolonged release drugs must now be preference to further reduce the risk for individuals in care. During COVID-19, addicts maybe exposed to additional risks [1]. Special emphasis should be given to improving harm reduction strategies to the addicts during COVID-19 period. The controlled and sustained release of addiction curing substances is also one of the strategies which will reduce some side effects [8]. Drugs used for the treatment of various pains are generally misused as addiction compounds. These are generally, opioid based compounds which are highly addictive and potentially lethal drugs. These drugs have killed thousands of peoples each year and thousands more struggling with addiction [9]. Despite of substantial advances in understanding of addiction mechanism and technology, the therapeutic approaches used for the de-addiction are still remained a major issue of serious concern. The major point of concern is that the compound used for addiction therapy is themselves become addictive in nature when used in higher concentration for longer time and start acting as abused substances [10]. Hence, some controlled and sustained drug delivery systems are required for the delivery of these compounds and bioadhesive polymer based buccal drug delivery systems specially based on polysaccharide can act as potential candidate for the same [11]. It has been found that the mucoadhesive drug loaded patches has maintained the drug concentration for a longer time and patches has not exerted any adverse effect on buccal tissue. These drug delivery carrier has been used for many oral infections, and other oral lesions [12]. Kowalski and coworker [13] have carried out the grafting of the poly (acrylic acid) onto methylated pectin and swelling of the hydrogel was found dependent on cross linker (NNMBA) and pectin content. Increasing the content of the crosslinking agent causes a reduction in swelling. However, introduction of small amount of pectin to poly (acrylic acid) hydrogel has increased the swelling and further increase in pectin ratio during the hydrogel formation has decreased the swelling of the hydrogel. Furuishi and coworkers [14] have reported pantazocine monolithic polymer matrix based patches those were prepared with different polyacrylate copolymers. These drug loaded patches were very effective for long term chronic pain. Generally transdermal drug delivery avoids hepatic fast-pass metabolism and a reduces the frequency of drug administration for better patient compliance.

Pentazocine is an opioid analgesic that has mixed opioid agonist and antagonist actions. It is used for relief of moderate to severe pain. Its short half-life requires frequent dosing in order to maintain the optimal therapeutic concentration due to its high metabolic rate. Repeated injections over long periods may cause fibrotic changes in the skin and muscular tissue. It has a low abuse potential and is not controlled by narcotic regulations [15]. Misuse of pentazocine can cause addiction, overdose, or death. It is also responsible for a strong psychological and physical dependence [16, 17]. Shu and coworkers [18] have found that high-doses of pentazocine antagonize the antinociception induced by a high-dose of morphine in a dose-dependent manner, and this antagonistic effect is not associated with the activation of kappa-opioid receptors.

Psyllium and pectin are gel forming polysaccharides and have been used as therapeutic and drug delivery agent. These are safe for oral administration, and have been used as excipient in food and pharmaceutical industry [19, 20]. Polyacrylic acid is a hydrophilic, pH responsive, gel forming mucoadhsive polymer which has been as a material for various biomedical applications including drug delivery applications [21]. In the present work pantazocine was used as model anti-addiction drug and its controlled and sustained release from psyllium/pectin/poly (AAc) based polymer has been determined. In view of the above facts, the present work is an attempt to design the drug delivery carrier for the sustained delivery of pantazocine from buccal patches to improve anti-addiction therapy during COVID-19 pandemic.

METHODS

Materials used

Psyllium [Sidpur Sat Isabgol Factory-Gujrat, India], pectin [Sisco Research Laboratories Pvt.Ltd. Mumbai India], acrylic acid (AAc) [Merck Specialities Private Limited, Mumbai-India], N, N'-MBA [Acros Organics, New Jersey-USA]. The model drug pentazocine lactate [BiosansLifecare- Kandivali, Mumbai, India] was procured from the market was used as received.

Synthesis of psyllium-pectin-poly (acrylic acid) polymer

Synthesis of polymer was carried out by co-polymerization reaction. The homogenous solutions of definite concentration of psyllium (1.25% w/v) and pectin (1.25% w/v) were prepared in a beaker after two hrs hydration. The initiation of polymer reaction was carried out by using definite concentration of ammonium persulphate (1.01×10^{-2} mol/L) taken in a reaction system containing definite concentration of monomer acrylic acid (9.11×10^{-1} mol/L), cross-linker NNMBA (2.98×10^{-2} mol/L) and glycerol (2% w/v) along with psyllium and pectin solution. The reaction mixture was then transferred to the petri plate and polymer film was prepared by solution casting method at 55°C. The dried named as Pecco-Psy-cl-poly (AAc) polymer (dry form) and hydrogel in wet form. The polymers prepared were used to study drug release and biomedical properties.

Swelling, drug release and biomedical properties of the drug carriers

Swelling was determined by using gravimetric method [22]. The loading of the drug pantazocine (a model anti-addiction drug) to the polymers and release of the drug from the drug loaded polymers was determined from the standard curve prepared by using on UV-Visible Spectrophotometer. Buffer solutions of pH 2.2, PBS and SWF were prepared according to the procedure reported in Indian Pharmacopoeia (Indian Pharmacopoeia Committee). The drug release diffusion mechanism was evaluated by using Ritger and Peppas equation [$(M_t/M_\infty)=kt^n$] [23] . Where M_t/M_∞ is the fractional release of drug in time 't', 'k' and 'n' are constants. M_t and M_∞ is drug released at time 't' and at equilibrium swelling respectively. The drug release profile was applied in different kinetic models, i.e. zero order, first order, Higuchi square root law,

Korsmeyer-Peppas model and Hixson-Crowell cube root to find out the best fit kinetic model for the release of drug from drug loaded hydrogels [24, 25].

The blood compatibility studies of the polymers were carried out by evaluating the thrombogenicity and haemolytic potential of polymers [26-28]. Thrombogenicity is determined by evaluation of the thrombus formation on the polymer surface and it was carried out by using the gravimetric method [29]. The haemolytic potential of the material is defined as the measure of the extent to which haemolysis of the blood can occur when it came into contact of polymers.

Antioxidant activity of polymers was evaluated by employing the 2,2'-diphenyl-1-picrylhydrazyl [DPPH] radical scavenging assay and Folin-Ciocalteu (F-C) reagent assay [29-31]. All the tests were carried out in triplicate.

Mucoadhesion studies of polymers with goat intestinal mucosa were carried out by using a Texture Analyzer equipped with a 5kg load cell and maximum detachment force (F_{max}) in N; and work of adhesion (W_{ad}) in N mm was determined [32].

Table 1: Results of diffusion exponents 'n' gel characteristics constant 'k' various diffusion coefficients release kinetics parameters and coefficients of different models for release profile of pentazocine lactate from drug loaded Pec-co-Psy-cl-poly(AAc) polymers, in different mediums at 37oC.

		pH 2.2 buffer	DW	PBS	SWF
Diffusion exponent 'n'		0.63	0.60	0.60	0.44
Gel characteristics constant 'k' $\times 10^2$		2.28	2.50	2.59	7.74
Zero Order Model:	R^2	0.91	0.95	0.96	0.84
$K_o \times 10^3 (min^{-1})$		1.90	1.80	1.87	1.71
First Order Model:	R^2	0.99	0.99	0.98	0.95
$K_1 \times 10^2 (min^{-1})$		0.57	0.48	0.55	1.23
Higuchian Model:	R^2	0.97	0.99	0.99	0.92
$K_H \times 10^2 (min^{-1})$		5.26	4.92	5.12	4.79
Korsmeyer-Peppas Model:	R^2	0.96	0.99	0.99	0.94
$K_{KP} \times 10^2 (min^{-1})$		2.28	2.50	2.58	7.74
Hixson-Crowell's Model:	R^2	0.98	0.99	0.99	0.97
$K_{HC} \times 10^3 (min^{-1})$		1.29	1.14	1.28	1.95

Where **Pec-*co*-Psy-*cl*-poly(AAc) = psyllium-co-pectin-cl-poly(acrylic acid)**

DW = Distilled water, PBS = Phosphate buffer saline, SWF = Simulated wound fluid,

Table 2: Results of thrombogenecity, haemolytic potential, mucoadhesion test, antioxidant activity of Pec-*co*-Psy-*cl*-poly(AAc) polymers

Variables				**Inference**
Thrombogenesis				
Weight of clot (g)	0.604 ± 0.02 g			Non-thrombogenic in nature.
Positive control	0.501 ± 0.07 g			
Negative control	0.005 ± 0.004 g			
Thrombose percentage (%)	122.34 ± 18.19 %			
Hemolysis				
Absorbance (540 nm)	0.8213 ± 0.023			Non-Haemolytic in nature.
Positive control	4.402 ± 0.18			
Negative control	0.647 ± 0.06			
Haemolytic index (%)	4.64 ± 0.71 %			
Ex-vivo mucoadhesion				
Peak detachment force	0.107 ± 0.07 N			Mucoadhesive in nature.
Work of adhesion	0.221 ± 0.029 N.sec			
Antioxidant activity				
F-C reagent assay		**DPPH assay**		
Antioxidant activity	10.10 ± 0.54 µg GAE	**Time**	**% inhibition**	Antioxidant in nature.
		2 hrs	07.97 ± 1.48	
		4 hrs	13.06 ± 0.69	
		8 hrs	20.17 ± 1.58	
		12 hrs	26.14 ± 2.47	
		24 hrs	45.44 ± 3.34	

DPPH assay = 2,2'-diphenyl-1-picrylhydrazyl assay and **F-C reagent assay** = Folin-Ciocalteu reagent assay

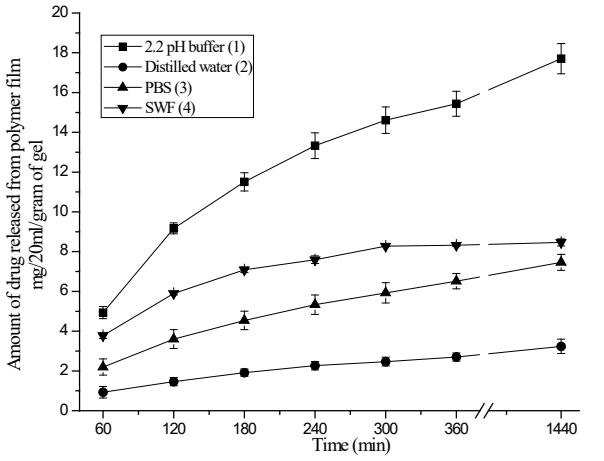

Figure 1: Release profile of analgesic drug pentazocine lactate from drug loaded Pec-co-Psy-cl-poly(AAc) hydrogels in different medium at 37oC.

RESULTS

Swelling and drug release from the drug carries

The results of the swelling of the drug delivery system are presented Table 1 and Fig 1. The diffusion exponent 'n', gel characteristic values 'k' values are presented in Table 1. The results of the biomedical properties of the drug delivery systems like haemocompatible, mucoadhesive and antioxidant are shown in Table 2.

DISCUSSION

Swelling and drug release from the drug carries

In general, swelling of the hydrogels decreased as the concentration of the acrylic acid increased during the formation of the hydrogels. However, the polymer formed with the lower concentration, some degree of polymer degradation was observed during the swelling of hydrogels. The swelling was observed higher in pH 7.4 buffer solutions as compared to the pH 2.2 buffer. This may be due the partial ionization of the polymer matrix and ionic repulsion in the polymer matrix that increased the pore size and swelling [33]. The swelling of hydrogels followed non-Fickian diffusion mechanism in case of polymers prepared with higher monomer concentration.
The results of release profile of pentazocine from drug loaded Pec-co-Psy-cl-poly (AAc) polymer in solution of different pH are presented in Figure 1. The release of drug from the polymer matrix was observed higher in solution of lower pH as compared to the higher one. This may be due to the more solubility of drug in acidic medium [34]. Here in this case, solubility of the drug was dominating factor over swelling of hydrogels for the diffusion of the drug during evaluation of drug release profile. The drug release has occurred by non-Fickian-diffusion mechanism in most of the cases. The release of drug profile is best fitted in to Hixson-Crowell model wherein the release of drug the area of the polymer based drug delivery devices. Furthermore, drug release did not show burst effect and release occurred in controlled and sustained manner. This may be due to the superamolecular interactions between drug and polymer films. In general, drug release from a polymeric system takes place by migration of the drug to the releasing medium that surrounds the drug loaded polymeric system, and drug solubility is an important factor in controlling its release from the polymer matrix [35]. Verma and coworkers [36] reported the hydroxypropyl methylcellulose based transdermal delivery systems of pantazocine. Burst release was observed with all formulations, which could be attributed to the direct exposure of matrix films to dissolution media. In another research report, a buccoadhesive polymer formed by addition of carbopol in hydroxypropyl methylcellulose has developed drug delivery system for the pentazocin with improved drug delivery profile [37]. However, in the present case, no burst release was observed and release occurred in controlled and sustained manner.
Recently, it has been found that the slow release formulations of opioids have overcome the drawbacks related to the conventional treatment used in case of chronic pain [38]. The extended drug release of fentanyl formulation enhanced the pain management and provided sustained pain relief while avoiding multiple dosing. The risks associated conventional formulations could be alleviated through controlled release of opioid [39, 40]. Hegde and coworkers [39] in their review of literature clearly mentioned that *"Many long-acting preparations developed in recent years do have the scope for becoming useful in everyday clinical practices"*.
Samaha, Robinson [41] have attempted to found the answer for the problem that "*Why does the rapid delivery of drugs to the brain promote addiction? and they concluded that rapidly delivered drugs might promote addiction by promoting forms of neuro-behavioural plasticity that contribute to the compulsive pursuit of drugs*". Hence controlled and sustained delivery of anti-addiction drugs from drug loaded drug delivery systems could exert of various benefits especially in case of drugs like pentazocine to improve anti-addiction therapy during COVID-19 pandemic.

Blood compatibility studies

The results of the thrombogenicity and haemolytic index for drug delivery system indicated thrombose percentage and haemolytic index as 122.34 ± 18.19 % and 4.64 ± 0.71 % respectively. Hence, these polymers were found to be thrombogenic and non-haemolytic in nature (ASTM, 2000). Hence, these polymers are regarded as safe for drug delivery applications.

Antioxidant activity

The results of the antioxidant activity of the polymers evaluated by the DPPH radical scavenging assay and F-C reagent assay showed 45.44 ± 3.34 % DPPH radical scavenging after 24 hours and antioxidant activity equivalent to (10.10 ± 0.54 µg) gallic acid respectively. The good antioxidant activity showed by functionalized polymers imparts peculiar characteristics to macromolecules of natural origin for specific biomedical application.

Mucoadhesion studies

The mucoadhesion studies of Pec-co-Psy-cl-poly(AAc) polymers showed that the F_{max} and work of adhesion values for

were 0.107 ± 0.07N and 0.221 ± 0.29 Nmm respectively (Table 2). Thus polymers were found to be mucoadhesive in nature. Mucoadhesion is the ability of the synthetic and biological macromolecules to adhere to the mucous membrane that makes the polymer drug delivery device site specific.

CONCLUSIONS

From the foregone discussion, it is concluded that the release of drugs from the drug loaded hydrogels occurred slowly without any burst release. The release of pentazocine that is used as a model anti-addiction drug, from the polymer matrix occurred in controlled manner. The release profile followed Non-Fickian diffusion mechanism and release profile was best fitted in Hixon-Crowell kinetic model of drug release. Overall, the polymers were found pH responsive, haemocompatible, mucoadhesive and antioxidant in nature and can be utilized as buccal patches to improve anti-addiction therapy. This will overcome the draw backs associated with the conventional formulations of the anti-addiction drugs. Overall, both, COVID-19 and addiction have formed the dangerous duo which fueled each other's propagation. During this period of disastrous pandemic, all the nations should address the various issues of the addicts with the utmost care. Further, controlled and sustained delivery of anti-addiction drugs from drug loaded drug delivery systems could exert of various benefits especially in case of drugs like pentazocine to improve anti-addiction therapy during COVID-19 pandemic.

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ETHICAL STATEMENT

The study is approved by ethics committee of Himachal Pradesh University.

CONFLICTS OF INTEREST

Authors have no conflict of interests

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AUTHORS' CONTRIBUTION

Man Mohan is Ph.D Scholar, and he has performed this study under the supervision of Dr. Baljit Singh who is a Professor in Department of Chemistry, Himachal Pradesh University Shimla-India.

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