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CONTROLLED RELEASE OF A POORLY WATER SOLUBLE DRUG PREDNISOLONE FROM HETERODISPERSE HYDROGEL SYSTEM

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ABSTRACT

The main objective of the present study is to prepare controlled release dosage form of prednisolone, a poorly water soluble drug. It is well known that certain moderate to poorly soluble drugs present difficulties, which render them incapable for sustained release formulations. To overcome this problem, a heterodisperse hydrogel system was formulated, which includes sustained release excipient including a gelling agent, an inert pharmaceutical diluent, an optional cationic cross linking agent and a poorly water soluble drug i.e. prednisolone. The results obtained indicated that acceptable 24 h release formulation may be obtained by this method.

KEYWORDS

Prednisolone, controlled release dosage form, heterodisperse hydrogel system.

INTRODUCTION

The advantages of controlled release products are well known in pharmaceutical field and include the ability to maintain a desired blood level of a medicament over a comparatively longer period of time and enhance patient compliance by reducing number of doses. Oral controlled release delivery system should ideally be adaptable so that release rate and profiles can be achieved to physiological levels.Oral formulation of poorly water soluble drugs often provide limited bioavailability if dissolution is rate limiting step in the overall absorption process[1]. Design of sustained release dosage form for some of these drugs is challenging because of their low solubility and dissolution rates[2.] An example of poorly soluble drugs is prednisolone, which often exhibit poor bioavailability, when incorporated into sustained release formulation[2-3]. Accordingly, a great deal of attention has been given to the preparation of sustained release prednisolone formulation which provides acceptable release[2,4]. Drug carrier systems such as cross-linked carmellose sodium, drug-cyclodextrins complex and surfactants have already been used in hydrophobic matrices to modify the dissolution behaviour of poorly water soluble drugs[5-7] .Previously, a heterodisperse polysaccharide excipient system has also been described in US patent US 4,994.296, US 5,128,143, US 5,135,757 and US 6,136,343.

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HETERODISPERSE HYDROGEL SYSTEM

Monolithic devices or matrices represent a substantial part of the drug delivery system. Matrices containing swellable polymers are also referred to as hydrogel systems. The term 'heteropolysaccharide' as used is defined as a water soluble polysaccharide containing two or more kind of sugar units, the heteropolyssacharide have a branched or helical configuration, excellent water wicking properties and immense thickening properties. An especially preferred heteropolysacharide is xanthan gum, which as high molecular weight .The other preferred heteropolysaccharide include derivative of xanthan gum. The homopolysaccharides gums, which are capable of cross linking with the heteropolysaccharide include galactomannans i.e. polysaccharides which are composed solely of mannose or galactose. Examples of homopolysaccharides gums are guar gum, locust bean gum, hydroxypropyl guar gum.

It has been found that a sustained release excipient comprising only of the gelling agent (heterodisperse, polysaccharide, e.g. xanthan gum and guar gum) may not be sufficient to provide a 24h formulation, nor to prevent an initial burst of drug release from the formulation, when the formulation is exposed to a fluid in an environment of use e.g. an aqueous fluid or gastrointestinal fluid. This is especially the case with certain drugs which are poorly soluble. This problem can be overcome by a discovery that by including a cationic cross linking agent in the sustained release excipient, the gel strength of the formulation can be a significantly increased. The release properties of the controlled release formulation may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharides gum is about 1:1 Although an acceptable slow release product is obtained when concentration of the heteropolysacharide gum is about 20 to about 80 percent in excess of homopolysaccharide. Some of the excipient such as xanthan gum are self –buffering in nature hence insensitive to the solubility of the drug and pH changes along the length of gastrointestinal tract.The inert filler of the sustained release excipient preferably comprise a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide or a polyhydric alcohol .Example of suitable inert fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol etc. The cationic cross linking agent, which is optimally used, may be monovalent or multivalent metal cation. Specific example includes calcium sulphate, sodium chloride, potassium sulphate, sodium carbonate, lithium chloride, sodium borate, potassium bromide, sodium bicarbonate, calcium chloride, calcium lactate, magnesium sulphate and sodium fluoride. The sustained release excipient is granulated with water or it may be further modified by granulating with hydrophobic material like ethylcellulose or eudragit RS and eudragit RL. Once the sustained release excipient has been prepared, it should be blended with the medicament. It has been found that it is important to include an effective amount of a wetting agent in the formulation in order to increase the bioavailability of drugs with poor solubility. An effective amount of any generally accepted pharmaceutical lubricant like magnesium state can be added. The sustained release excipient is free flowing and directly compressible. Accordingly, the excipient may be mixed in desired proportion with therapeutically active medicament and optimal lubricant. Alternatively, all or part of the excipient may be subjected to

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wet granulation with active ingredient and thereafter tableted [8-10]. The main objective of the present work is to provide sustained release excipient, which may be used in the preparation of sustained released oral dosage form of poor water soluble drug like prednisolone.

MATERIALS AND METHODS:

Prednisolone was procured from Paam Pharmaceuticals Ltd, Delhi, India. Xanthan gum, lactose, HPMC were supplied by commercial sources. Other materials used in this study were of analytical grade.

Preparation of heterodisperse hydrogel system:-
For the preparation of heterodisperse hydrogel, sustained release excipients were prepared, medicament was added subsequently and then the final mixture was tabletop. The sustained release excipient was prepared by dry blending the requisite amount of xanthan gum, guar gum, calcium sulphate and dextrose in a pestle mortar. Then water was added to the dry blended mixture and dough was prepared. The granules were prepared by passing dough through 20 mesh screen .The ingredient used for the granulation of various batches are given in Table 1.

Table 1

Composition of sustained release excipient

Batch	Composition (%w/w)			
	Xanthan gum	Guar gum	Calcium sulphate	Dextrose
A	25	25	0	50
B	25	25	5	45
C	25	25	20	30

The sustained release excipients prepared were dry blended with the desired amount of prednisolone along with suitable amount of wetting agent (PEG 4000). Then a suitable lubricant was added and tablets of average weight 300mg were prepared.

Tablet formulation composition

Sustained release excipient	83.3%
Prednisolone	6.7%
PEG 4000	8%
Magnesium sterate	1%
Talc	1%

Preparation of controlled batch
Control batch of Prednisolone was prepared by direct compression by using HPMC as release retardant, with which all other batches of heterodisperse hydrogel system were compared. Each tablet prepared was of 300mg**.**

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Composition of control batch:

Prednisolone	6.6%
Lactose	66.4%
HPMC	25%
Magnesium sterate	1%
Talc	1%

Physical characterization

The fabricated tablets were characterized for weight variation (n=20), hardness (n=6, Monsanto hardness tester), % friability (n=20, Roche friabillator, electrolab, Mumbai, India) and drug content.

In vitro released studies

The drug release was evaluated by carrying out in vitro dissolution studies in HCL buffer of ph 1.2 and phosphate buffer of pH6.8 using type II dissolution apparatus (paddle type). The effect of rotation (100 rpm), temperature of the bath (37.0± 0.5°C) and the volume of dissolution medium (900 ml) were kept constant throughout the study. At the predetermined time intervals, 5 ml of the samples were withdrawn and filtered through 0.45µ membrane filter and diluted to a suitable concentration and then immediately analyzed. Absorption of these solutions was measured at 242 nm by using shimadzu UV - 1700 UV/VIS double beam spectrophotometer (Kyoto, Japan). Appropriate correction factor was applied and percentage release was calculated. The release mechanism of various batches was illustrated using ZOREL software

Stability studies:

The best batch was subjected to stability studies at 40±2°C/75±5% RH for 3 months according to ICH guidelines. Sampling was done after 1, 2 and 3 months .The formulation was evaluated for organoleptic characters, hardness, drug contents and dissolution studies.

RESULTS AND DISCUSSION

Weight variation data of the prepared batches indicated no significant difference in the weight of individual tablet from the average value. Hardness of the prepared tablets was observed to be with in the range to 4.5-5.5 kg/cm^2. Friability of all the tablets was found below 1%. The drug content in all the batches of prednisolone tablets was in the range of 98.21 to 99.54. This ensured the uniformity of the drug content in the tablets.

Release studies showed that in case of control tablets i.e. matrix tablets containing pure Prednisolone and HPMC, release of drug was not complete. It was found to be 51.93±0.35% in buffer of pH1.2 and 52.92±0.17% in buffer of pH 6.8. This can be attributed to poor solubility and slow dissolution rate of prednisolone. In case of tablets containing sustained release excipient i.e. heterodisperse hydrogel system, gums were able to sustain the drug upto 24 h. Batch A, B and C released 88.23±0.02%, 83.49±0.38% and 77.69±0.43% drug after 24 hours in buffer of pH1.2 and 87.85±0.55%, 86.15±1.18% and 76.52±1.75% in buffer of pH 6.8, i.e much more than control batch. This may be due to swellable properties of polymers used, which formed hydrogel system. It has already been reported that

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heterodisperse excipient comprises a gelling agent of both hetero and homo-polysaccharide which exhibit synergism e.g. the combination of two or more polysaccharide gum produce a higher viscosity and faster hydration than that which would be expected by either of the gum alone, the resultant gel forms at rapid rate and is more rigid[10]. It was also found that with the use of cationic cross linking agent i.e. calcium sulphate in sustained release excipient, drug release gets further decreased. The release profile of all the batches of tablet is represented in Figure 1 and 2.

Figure 1

Release profile of batch A, B, C and control batch in buffer of pH 1.2

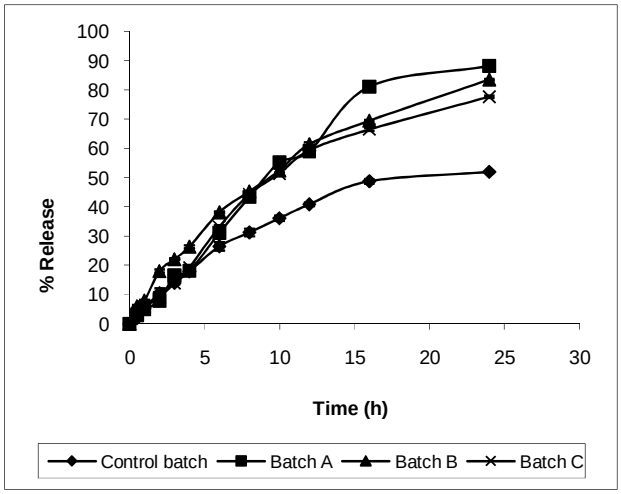
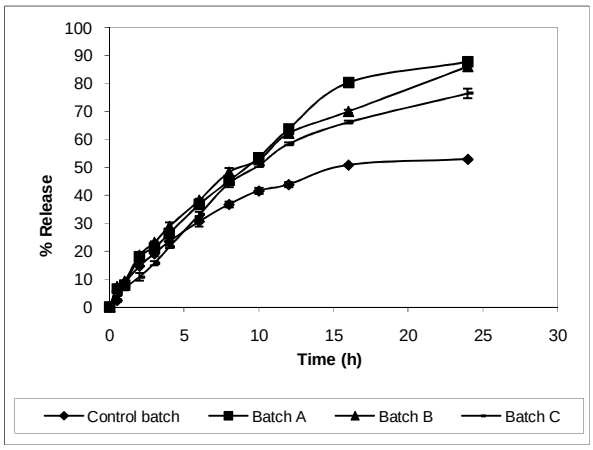


Figure 2

Release profile of batch A, B, C and control batch in buffer of pH 6.8



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Release Mechanism:

The results of ZOREL showed that the values of exponent (n) ranged between 0.67-0.95 for various batches. As all these n values are greater than 0.45, the mechanism of drug release is distinctly non-fickian diffusion. But for those batches which have a values of n>0.85, the mechanism of drug release is zero order. The dissolution parameters like n, K_1, K_2, $t_{50\%}$, $t_{60\%}$, $t_{70\%}$, $t_{80\%}$, $t_{90\%}$, overall release for all formulation are presented in Table 2.The results indicated zero-order release profile of batch A and C and released observed with batch A, B, C was much more than the control batch. So batch A was selected as the best batch as it released 88% drug in 24 hrs in controlled manner. To find out the influence of pH on best selected formulation, t-test was applied, t_{cal} was found to be less than t_{tab} .This showed that the influence of pH on the formulation was insignificant.

Stability studies:

The Batch A was subjected to accelerated stability testing to determine the changes in physiochemical characteristics of the formulation. There was no change in organoleptic characteristics, hardness and drug content. Dissolution studies also showed no significant change after storage for 3 months (Figure 3).

Figure 3

Release profile after stability studies

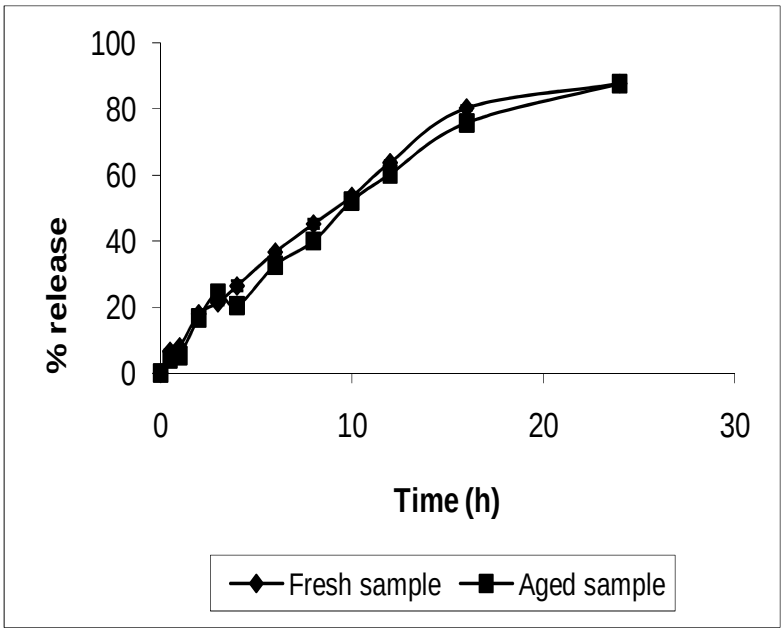

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Table 2
Dissolution parameters obtained by ZOREL software

Formulation	K_1	K_2	$t_{50\%}$	$t_{60\%}$	$t_{70\%}$	$t_{80\%}$	Overall rate of Drug release	% Drug release	Order of release
Batch control (1.2pH)	1.0263	0.0355	---	---	---	---	0.660±0.358	51.93%	Non Fickian (n=8409)
Batch control (6.8 pH)	1.0583	0.0297	- --	---	---	---	0.784±0.661	52.92%	Non Fickian (n=0.7671)
Batch A (1.2pH)	0.9851	0.0711	10.472	12.671	14.8887	17.117	0.906±0.487	88.23%	Non Fickian (n=0.9567)
Batch A (6.8 pH)	1.056	0.0516	9.228	11.833	14.602	17.519	1.053±0.686	87.85%	Non Fickian (n=0.7296)
Batch B (1.2 pH)	1.058	0.0477	9.560	12.281	15.177	8.232	1.017±0.628	83.49%	Non Fickian (n=0.7256)
Batch B (6.8 pH)	1.076	0.0432	9.329	12.5211	15.323	18.673	1.069±0.743	86.15%	Non Fickian (n=0.6783)
Batch C (1.2 pH)	1.0078	0.0585	11.217	13.827	16.501	---	0.875±0.376	77.69%	Zero order (n=0.8761)
Batch C (6.8 pH)	1.0257	0.0524	11.161	14.012	15.985	---	0.907±0.428	76.52%	Non Fickian (n=0.803)

K_1=Fickian contribution constant
K_2=Case II Relaxation Contribution Constant

CONCLUSION

To increase the therapeutic efficacy of prednisolone, heterodisperse hydrogel system was prepared, which was able to sustain drug upto 24 hours with sufficient release. So it is speculated that by formulating heterodisperse hydrogel system, it is possible to obtain a formulation having a more constant plasma concentration

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