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Targeting various sites of gastro intestinal tract using cellulose acetate pthalate and carbopol polymer

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ABSTRACT

Double compression of the wet granulated powders formulated using Cellulose acetate pthalate(CAP) and carbopol as pH sensitive polymers. The drug (paracetamol) were divided into three parts were one part treated as immediate dose and forms a single layer and the remaining as CAP and carbopol collectively as second layer. This second layer were compressed over the precompressed immediate layer thus giving a combination of immediate release and a sustained release. The invitro release and invivo release- urinary relase data showed a positive response thus substantiating the release of drug contents at gastric pH, duodenal pH and the distal intestinal part. This tablet could be a good candidate for targeting the parts of GIT. This enhances the drug delivery and decreases the adverse reaction of the drug to a great extent.

INTRODUCTION

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacologically active moieties using novel drug delivery system. The duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecule inherent kinetic properties. Thus optimal design of controlled release system necessities a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug[1]. The primary objective of the controlled delivery is to ensure safety and improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

pH sensitive polymers[6] were dissolved at biological fluids at different fluids at different rates in various different parts of the digestive system. Various studies were conducted about pH sensitive polymers. A formulation containing cellulose acetate pthalate for preparing enteric coated granules was developed with the use of

granulation techniques. The human gastro intestinal system consists of three distinctive parts,

(a) Stomach

(b) Small intestine duodenum, jejunum,ileum

(c) Large intestine

The stomach secretes about 2 liters of gastric juice daily from the secretary glands in the mucosa, which has the ph range between 1.5 to3.5 in which most of the drugs are released.

The small intestine comprises three main sections,

(a) Duodenum

(b) jejunum

(c) ileum

The secretion from the gall bladder and pancreas are released in to the duodenum through hepatopan creatic ampulla and consists of water, mineral salts and enzymes amylaseand lipase.

CAP was selected as the polymer of enteric coating because it particularly dissolves at the non enteric part of GIT[5]. The pancreatic juice is alkaline because it contains significant quantities of bi carbonate ions which are alkaline in solution. When acid stomach contents enter the duodenum they are mixed with pancreatic juice and bile and the ph is raised to between 6 and 8.Alkaline intestinal juice (ph 7.8 to 8)assists in raising the ph of the intestinal contents to between 6.6 to 7.5.So in the small intestine the pancreatic juice with bile and intetinal juicevaries the ph at duodenum and rest of the parts in the intestine, so CAP can be used as the polymer to release the drug in the distal end end of the duodenum where the ph is >6 and below which the alkaline intestinal juice varies the ph were carbopol[4] is the suitable polymer to release the drug in a sustained delivery form.

EXPERIMENTAL

Double compressed tablet of paracetamol were formulated using immediate release wet granulated powders as one layer and pH sensitive release (Cellulose acetate Pthalate -CAP and Carbopol Layer)as another layer. The drug were divided in to three doses were each dose is mixed with immediate release, CAP and carbopol respectively.The excipients used were starch , lactose, Starch mucilage as the binder, Talc and magnesium stearate.Only a small quantity is permissible the binder is blended in with the dry powders intially. When a large quantity is required the binder is usually dissolved in the liquid. The solubility of the binder also has an influence on the choice of methods since the solution should be fluid enough to disperse readily in the mass.

After the granulation they are sieved through sieve number 60 and dried at 60^0C.Then those granules are then sieved through sieve number 22 and dried at 40^0C. The wet screening process involves converting the moist mass in to coarse granular aggregates by passage through a hammer mill or oscillating granulator equipped with screens having large perforations. The purpose is to further consolidate granules increase particle contact points and increase surface area to facilitate drying.

Overly wet material dries slowly and forms hard aggregates that tend to turn to powder during subsequent dry milling. There are many instances in which wet milling may be omitted with a considerable saving of time. The formulator should be alert to these opportunities and not follow the old method blindly. A drying process is required in all wet granulation procedures to remove the solvent that was used in forming the aggregates and to reduce the moisture content to an optimum level of concentration with in the granules.

Double compression

There are two classes of multiple compressed tablets layered tablets and compression coated tablets. Both types may be either two components or three-component system. Two or three layered tablets a tablet with in a tablet or a tablet with in a tablet with in a tablet. Both types of tablets usually undergo a light compression being the final one. In this experiment, the immediate release layer is pre compressed using minimal pressure (cadmach 16 station-model no 14512). The enteric retarding layer CAP layer is mixed with Carbopol layer and placed over the precompressed immediate layer. Then using the permissible maximum pressure the tablet is compressed.

Evaluation[2]

In vitro evaluation were carried using basket type dissolution apparatus with paddle stirrer ar an RPM of 100 in temperature 37^0C. The dissolution medium were 0.1 N HCL for the 4 hour. Then the dissolution were carried at solution of pH 7.5(Enteric retardent effect)

and at pH 8(for sustained release) for about 4 hours respectively. The hardness of the tablet was evaluated using Monsanto hardness tester and the friability test were carried using roche friabilator apparatus. Weight variation were also carried. The urinary excretion studies were also carried out as follows. The drug was administered orally by breaking the tablet in to smaller pieces and subsequently water has been provided to swallow the given tablet to the male wurstar rat. Urinary analysis was done which is one of the in vivo test to prove the S.R. action of the formulation by using the amount urine collected and subjecting them to the U.V spectrum[3].

Two different formulations were selected in which one of the formulation containing the drug with polymer is given to one of the healthy male rat(test) and another drug with out polymer was given to another healthy male rat (control) which were provided with lot of water. The urine has been collected at time intervals of 1hr, 2hr, 3hr and 4hr respectively on both test and control were analysed through U.V spectro photometer.

RESULTS

The *in vitro* dissolution release of the formulated double compressed tablet at various dissolution media were given in the following TABLE 1.

The friability of the punched tablet were found to be 0.18%w/w, the hardness ranges from 5-5.5kgs/cm^2. The weight variation were found to be in the range of 0.01% to 0.3%.The *in vivo* urinary analysis were also carried out as mentioned earlier. The U.V spectrum analysis of the (control) sample shows the continuous decrease of the drug in the excreted urine as the time progressed but in the case of test, the U.V analysis shows the gradual increase in the drug in excreted urine when compared to that of control. This is evident from the following TABLE 2 and graph 2.

DISCUSSIONS

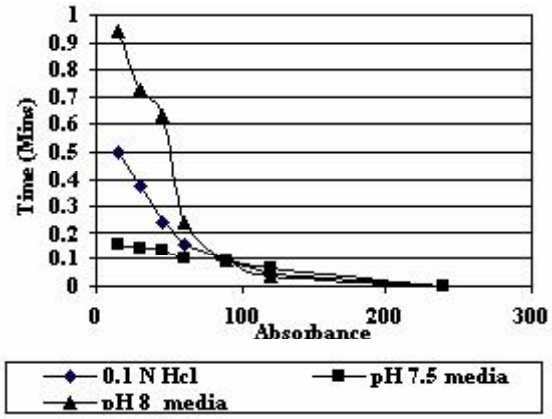
The tablet which has both I.D (immediate release) and S.R(Sustained release with polymers) where formulated and evaluated for their friability, hardness, and weight variations. The result of the friability were

TABLE 1: Dissolution of the double compressed tablet at various media

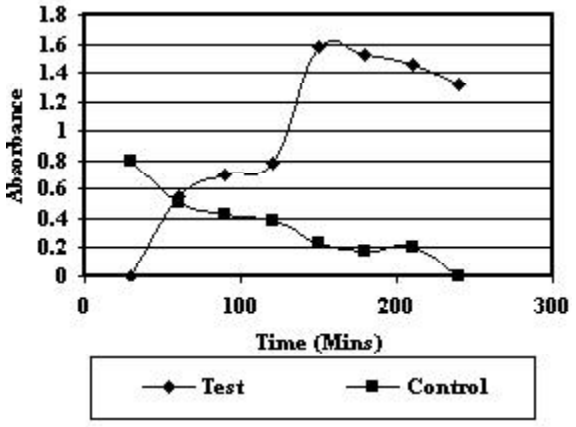
	Absorbance of the sample taken from the following media		
Time (minutes)	0.1 N Hcl	pH 7.5 media	pH 8 media
15	0.499	0.153	0.94
30	0.377	0.143	0.73
45	0.241	0.131	0.63
60	0.154	0.101	0.24
90	0.098	0.093	0.095
120	0.042	0.064	0.038
240	0	0	0

TABLE 2 : Urinary analysis of the drug

S.No	Time(mins)	Test	Control
	30	0.002	0.802
	60	0.551	0.511
	90	0.707	0.422
	120	0.79	0.38
	150	1.586	0.24
	180	1.521	0.18
	210	1.461	0.2
	240	1.32	0



Graph 1 : Dissolution of the tablet at various dissolution media



Graph 2 : Urinary analysis of the drug

0.18%W/W which is an acceptable and with in the prescribed limits. The hardness of the tablet, which was determined using Monsanto hardness tester showed and acceptable value thus proving the tablet to possess necessary mechanical strength. The weight variation of these tablets was evident to prove that those compressed tablets were of required weight. Tablet which was subjected to *in vitro* dissolution studies under varying ph, showed four hour instantaneous release at a ph 1.5-3 simulating stomach(gastric environment), for pH range 7.5(simulating duodenal environment and 8(simulating distal intestinal environment) showed an appreciable release. From these in vitro releases it was evident that I.D showed a release at a normal gastric pH. CAP polymer showed a normal instant release which latter decreased at a ph 7-8(duodenal environment) and carbopol, showed the same four hour release at pH greater than 8 (small intestinal environment) which latter decreased to a very low level. Thus at invitro condition both the immediate dose and the polymer loaded dose showed its release that is based on its pH of the dissolution media which gets completely exhausted within the period of four hours.

In urinary excretion analysis TABLE 2 and graph 2 the control (tablet with out polymer showed a constant decline which was initiated after1/2 hr) but in the test animal (tablet with polymer) showed an appreciable increase for about 1-1½ hrs. Which then showed a decline at second hour. but a sharp rise was observed after the second hour and the sustainity prevails.

Thus an initial increase may be due to I.D and initial sustainity may be due to the CAP polymer and the sudden decline of the urine drug level indicates the elapse of the CAP polymer and a shooting of drug level after second hour may be due to release of drug from carbopol polymer. Thus sustained swelling of the carbopol was evident from the S.R profile after 2½ hrs.

Therefore on the basis of invitro release at various pH medias and the *in vivo* release (Urinary data) it could be said that the polymer is efficient in targeting or dissolving at the respective pH environment thus targeting to the desired area of the G.I.T. This has a great impact in sustaining the drug release and in turn the pharmacological

CONCLUSION

This double compressed tablet is a real candidate for both targeting and sustaining the drugrelease in the gastro intestinal tract, which enhances the therapeutic activity of the drug and also has the ability to reduce any adverse effect.

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