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DESIGN AND DEVELOPMENT OF CONTROLLED RELEASE FORMULATIONS OF CARVEDILOL & DILTIAZEM HYDROCHLORIDE USING NATURAL GUMS

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Abstract:

Oral controlled drug delivery systems have evolved as a highly convenient and adaptable method of medication administration, considerably increasing patient compliance by reducing dosage frequency. Tablets, the ideal formulation for controlled release, provide high physicochemical stability and precise dosing, resulting in a consistent therapeutic effect. These systems are especially useful for addressing chronic illnesses because they give a prolonged flow of medication, increasing total treatment efficacy while minimizing side effects. The development of controlled release formulations has accelerated in recent years, spurred by the necessity to reformulate current pharmaceuticals and maintain market share in the face of a scarcity of new chemical entities. Recent advances in formulation design have resulted in a profusion of commercial controlled release products, indicating an increasing demand for effective drug delivery methods. Controlled release systems are distinguished by their capacity to sustain therapeutic drug levels over long periods of time, however genuine zero-order release remains a difficulty. Understanding the differences between sustained and controlled release is critical for optimizing drug administration, as the latter seeks exact temporal and spatial control over medicine release. These abstracts emphasize the importance of oral controlled drug delivery devices in current pharmacology and their ability to improve treatment results.

1.INTRODUCTION

Oral controlled drug delivery systems were found to be the most practical type of drug delivery systems because to their high patient compliance and flexibility in dose form design (Phvitra T. K, 2011). The most common method of administering drugs is orally, and tablets are the recommended formulation for precise dosing and great physicochemical stability in controlled drug delivery systems. These formulations have drawn a lot of interest lately and are very desirable since they give the patient a steady dose of the medication (Lordi N. G, 2001). The targeted medication dose, release profile, physiological parameters, and other factors determine the type of drug delivery systems. Because the frequency of dose is reduced with these dosage forms, patient compliance is increased (Rajesh G, 2001). When compared to two traditional release dosage forms, extended release formulations are intended to provide at least a twofold reduction in dosing frequency (Suman, K., 2009). Controlled release drug delivery systems are intended to improve the therapeutic benefits of the medicine, minimize its side effects, and provide

numerous advantages for managing the illness state (Shala J, 2006).

Many pharmaceutical companies are being forced to reformulate an existing conventional formulation into a controlled release product as a life cycle management strategy and to hold onto market shares due to the lack of new chemical entities (Marcel Dekker 1978). A growing number of patents, articles, and commercial controlled release devices for the distribution of various pharmacological chemicals demonstrate the substantial advancements made in the field of controlled release design during the previous few decades (Marcel Dekker 1978).

Any dosage form that delivers medication over an extended period of time is considered to be controlled release, and this indicates that the system is capable of providing some real therapeutic control, whether it be spatial, temporal, or both. This accurately points out that not all sustained release systems fall under the category of controlled release systems. In order to keep the drug's level in the tissues for a longer amount of time, sustained release dosages aim to achieve zero order release from the dosage form. The majority of sustained release devices do not achieve this kind of release and instead deliver the medication slowly via first-order release.

In other words, such medications are absorbed at a limited pace due to permeability or transmembrane. Pharmaceutical products developed for oral delivery are mostly traditional drug delivery systems, which are intended for instant drug release and rapid absorption.

2.LITERATURE SURVEY

1. Afrasim M, Shivakumar H G, Formulation and In Vitro evaluation of SustainedRelease Tablet of Diltiazem, Influence of Hydrophilic Gums Blends, Journal of Pharmacy Research, 2010; 3(3): 600-604.

Abstract: The aim was to develop sustained release matrix tablets of diltiazem hydrochloride (DTZ) using natural gums (Locust bean gum (LB) and Karaya gum (K)) as novel Hydrophylic matrix systems compared with the extensively investigated Hydroxypropyl methylcellulose [H]. Matrix tablets of DTZ were prepared with different ratio of drug: polymer (1:1, 1:2, and 1:4 of LB, LBK, LBH and LBKH) by direct compression. The matrix tablets were characterized for their hardness, friability, in vitro release study and percentage assay. Totally 12 different formulation were prepared. Tablets with only LB gum alone cannot control drug release. Locust bean gum on combinations with Karaya gum sufficiently controls the drug release, while combinations of LBH and KLBH exhibited high and low drug release efficiency respectively. Among the formulated formulations LBH was having the highest mean dissolution time (MDT) and least dissolution efficiency (DE 12%). The dissolution data was fitted into Higuchi and Korsmeyer equation. Diffusion exponent indicated the mechanism to be anomalous type that indicates the combination of diffusion and erosion mechanisms. Scanning electron microscopy (SEM) images of the tablets before and after dissolution showed the morphological changes confirming the release mechanism. DSC studies

confirmed that there was no chemical interaction between drug and polymer. Among all the formulation, F5 did not significantly differ compared to the marketed product with respect to drug release but other formulations differ significantly compared to the marketed product for $p< 0.05$. Results of the present study demonstrated that combination of the two natural gums could be successfully employed for formulating sustained-release matrix tablets. According to the similarity factor (f2), formulation F5 was comparable to the marketed formulation (Dilzem-SR).

2. Asha P, Nilam B, Patel K R, Patel N M, and Patel M R, Colon targeted drug delivery system: a review system, Journal of Pharmaceutical Science and Bioscientific Research, 2010; 1(1): 37-49.

Abstract: The administration of drugs orally provides tremendous advantages; patient compliance is one of them. Most pharmaceutical research has concentrated on oral drug delivery systems to avail these advantages. But oral drug delivery system has some demerits, including unpleasant side effects and poor effectiveness due to first-pass metabolism. This situation may urge the development of targeted drug delivery systems. Moreover, with a rise in the prevalence of colonic disorders worldwide and less effectiveness of conventional drug delivery systems, the development of colon-targeted drugs is required. The colon-targeted drug delivery system delivers the drugs to the colonic environment. It is highly desired to provide medications specifically to the colon for the local treatment of various intestinal illnesses. Several formulation strategies, such as pH-sensitive, enzyme-triggered, and magnetically-driven systems, have been explored to improve colonic medication delivery. Though the colon-targeted delivery system has few flaws, this delivery system provides tremendous advantages, particularly in managing colonic diseases. In light of the current prevalence of colonic diseases and the benefits of colon-targeted drug delivery systems over conventional methods, focusing more on colon-targeted drug delivery systems is essential.

3. Carvedilol loaded Mucoadhesive buccal tablets, Influence of various mucoadhesive polymers on drug release behavior, PDA Journal of Pharmaceutical science and Technology 2009: 63(3): 196-206.

Abstract: The major objectives of the current study were (i) to prepare carvedilol-loaded buccal tablets by direct compression technique, and (ii) to study the influence of low and high proportions of sodium carboxy methylcellulose (SCMC) in conjunction with the corresponding high and low proportions of sodium alginate, polyvinyl pyrrolidone (PVP-K-30), carbopol 974P, and hydroxypropyl methylcellulose (HPMC) on the basic properties (hardness, friability, weight variation, thickness uniformity, drug content, mucoadhesive strength, surface pH, swelling property, and drug release behavior) of the tablets. Altering the polymer combinations did not affect the physical properties of the buccal tablets. However, the presence of SCMC and sodium alginate at 1:2 ratio in the

tablet showed a sustained drug release. In addition, this polymer combination at 2:1 ratio did release the drug completely during the stipulated dissolution time. Swelling study indicated the tablet structure collapse over time at 2:1 polymer ratio, thus exposing the drug molecules directly to the dissolution medium to attain the complete drug release from the SCMC and sodium alginate-based tablets. On the other hand, whatever the polymer ratios, the SCMC and carbopol 974P combination always retarded the drug release in an almost similar manner. Though the SCMC- and carbopol 974P-based tablets did display an impressive mucoadhesion property, the surface pH value determined for this polymer combination was found to decrease considerably due to the liberation of the free carboxylic acid over the time period.

4. Diwan. P V, Rama Rao. P, Ramakrishna. S, Reddy. M N, Comparative in vivo evaluation of propranolol hydrochloride after oral and transdermal administration in rabbits, Eur. J. Pharma and Biopharma, 2003: 56: 81-85

Abstract: The purpose of this study was the in vivo evaluation of orally and transdermally administered propranolol hydrochloride in rabbits. Transdermal patches of propranolol hydrochloride (PPN) were formulated employing ethyl cellulose and polyvinylpyrrolidone as film formers. The pharmacodynamic (PD) and pharmacokinetic (PK) performance of PPN following transdermal administration was compared with that of oral administration. This study was carried out in a randomized cross-over design in male New Zealand albino rabbits. The PK parameters such as maximum plasma concentration (C(max)), time for peak plasma concentration (t(max)), mean residence time (MRT) and area under the curve (AUC(0-alpha)) were significantly ($P<0.01$) different following transdermal administration compared to oral administration. The terminal elimination half-life (t(1/2)) of transdermally delivered PPN was found to be similar to that following oral administration. In contrast to oral delivery, a sustained therapeutic activity was observed over a period of 24 h after transdermal administration compared to oral administration. The relative bioavailability of PPN was increased about fivefold to sixfold after transdermal administration as compared to oral delivery. This may be due to the avoidance of first pass effect of PPN. The sustained therapeutic activity was due to the controlled release of drug into systemic circulation following transdermal administration.

5. Hiroshi. Y, Takehikosuzuki, Masakazu. M, Kazuo. N, and Masa. Y S, In situ perfusion system for oral mucosal absorption in dog, Journal of Pharmaceutical Sciences, 1990; 79(11): 4.

Abstract: To evaluate oral mucosal absorption of drugs in dogs, a newly designed in situ perfusion system with a circulating perfusion chamber was developed. The utility of the perfusion system was investigated by using three drugs: salicylic acid (SA), sulfadimethoxine (SM), and diltiazem (DIL). The oral mucosal absorption of the drugs could be adequately described by

first-order rate processes. The absorption rate was independent of the amount of un-ionized drug, which varied with the pH of the solution. The absorption of SA was similar for various oral mucosal sites and for repeated experiments using the same site. Pharmacokinetic analysis for the plasma or medium concentration of SA after perfusion showed that SA was absorbed at the rate constant of 0.071 h-1, and that approximately 70% of SA absorbed from oral mucosa was transferred to the circulating blood.

3.METHODS:

1. In-vitro methods

An apparatus consisting of a water jacket and an internal compartment containing 50 ml of simulated saliva as dissolution medium to study the drug release by placing in the metal die sealed at the lower end by paraffin wax to ensure the drug release from one end alone. The medium was stirred with a rotating stirrer at 250 rpm. Novel dissolution apparatus also developed comprising of a single, stirred, continuous flow-through filtration cell that includes a dip tube designed to remove finely divided solid particles. Filtered solution is removed continuously and used to analyse for dissolved drug.

2. Ex-vivo methods

Most of the ex-vivo studies examining drug transport across buccal mucosa use buccal tissues from animal models. Immediately after sacrificing the animals the buccal mucosal tissue is surgically removed from the oral cavity. The membranes are stored in Krebs buffer at 4°C until mounted in the diffusion cells for the ex-vivo permeation experiments.

3. In-vivo methods

The rat has a buccal mucosa with a very thick, keratinized surface layer. The rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human tissue. Among the larger experimental animals monkeys are practical models because of the difficulties associated with its maintenance. Dogs are easy to maintain and less expensive than monkeys and their buccal mucosa is non-keratinized and has a close similarity to that of humans. Pigs also have nonkeratinized buccal mucosa similar to that of human and their inexpensive handling and maintenance costs make them a highly suitable animal model for buccal drug delivery studies.

4.CONCLUSION:

The results of the present investigation concerned with buccal tablets clearly indicated that the method employed for the production of buccal tablets greatly influence the permeability of carvedilol. Wet granulation technique was found to be a promising method for the preparation of buccal tablets for controlled release of carvedilol. The buccal tablets formulated with sodium alginate, gum karaya, pectin are more permeable than with the buccal tablets prepared with gum kondagogu. The resulting buccal tablets provided slow and controlled release of carvedilol over 8.5 hrs. Drug release from these buccal tablets can be controlled by changing concentration of gums in the preparation of the buccal tablets. The buccal tablets exhibited good controlled release characteristics during in vitro release. As such the buccal tablets are recommended for oral controlled delivery of carvedilol. Thus the present investigation resulted in

the development of buccal tablets for oral controlled delivery of carvedilol fulfilling one of the major objectives of the investigation.The results related to the colon tablets indicated that the concentration of gum kondagogu employed in the formulation influences the drug release rate. With increase in the concentration of gum employed in the preparation of colon tablets. Gum kondagogu was found to be a good colon forming material for controlled release of diltiazem hydrochloride over 18 hrs. Drug release from the colon tablets can be controlled by changing the amount of gum.

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