

EFFECT OF DIFFERENT ADDITIVES ON CELECOXIB RELEASE

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ABSTRACT

Aim: study the effect of addition of different additives such as hydrophilic polymers like (HP- β -CD, PVPK30 and Urea) by solid dispersion technique and hydrophobic polymers like (Ethyl cellulose and Cellulose acetate butyrate) by microencapsulation technique on release of Celecoxib.

Methods: solid dispersions for hydrophilic polymers were formulated in drug polymer ratio 1:2.5, 1:5, 1:7.5 and 1:10 using solvent evaporation method. The emulsion solvent-evaporation technique was used for hydrophobic polymers in drug polymer ratio 1:2, 1:4 and 1:6 for preparation of Celecoxib microcapsules. The prepared solid dispersions and microcapsules were examined for the production yield, the drug content, the micromeritic properties and in-vitro drug release.

Results: hydrophilic polymers improved dissolution of poorly water-soluble Celecoxib while hydrophobic polymers sustained the release of Celecoxib.

Conclusion: The best formula for the solid dispersion after in vitro release test was CXB-HP- β -CD (1:10), but for the microcapsules was CXB-EC (1:2).

Keywords: Celecoxib, Emulsion solvent-evaporation, Microencapsulation, Solid dispersion, Solvent evaporation.

INTRODUCTION

Celecoxib was our drug of choice which is the first specific inhibitor of cyclooxygenase-2 (COX-2). The aqueous solubility of CXB is low (3 to 7 $\mu\text{g}/\text{mL}$). The oral bioavailability of CXB is between 22% and 40%. Thus, it is important to enhance the solubility and dissolution rate of CXB to improve its overall oral bioavailability.

The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhance oral bioavailability [1].

Microencapsulation represents one of the methods by which modification of the release of the drug is achieved by delaying the time during which the drug is available and by retarding the attack of the gastrointestinal fluids. So, it is regarded as one of the most effective tools in formulating prolonged action dosage forms [2]. Emulsion-Solvent Evaporation method has been widely used and several modifications of the technique have been successfully employed for the encapsulation of drugs.

The aim of the present paper is to study the effect of addition of different additives as hydrophilic and hydrophobic polymers on CXB by solid dispersion technique and microencapsulation, respectively.

MATERIALS AND METHODS

Materials

Celecoxib kindly donated by Medical Union Pharmaceuticals, Abu Sultan, Ismailia, (Egypt). HP- β -CD (MW 1380), kindly donated by Medical Union Pharmaceuticals, Abu-Sultan, Ismailia, Egypt. PVPk30, Winlab Leicestershire, (United Kingdom). Urea, Alpha Chemical, Mumbai, (India). Methanol, PureLab, Madison, (USA). Sodium Lauryl Sulfate (SLS), Alnasr Pharmaceutical Chemical Co., (Egypt). EC (BIO BASIC INC, Markham, Ontario-3R1G6, Canada). CAB [9004-36-8], (ALPHA CHEMIKA Chemical Co., Mumbai-400 002, India). N-Hexane (pure lab. Chemicals, USA). Acetone (pure lab. Chemicals, USA). Sorbitan Monooleate (Span 80), Cuangdong Guanghua chemical Co., India. Light Paraffin Oil (pure lab. Chemicals, USA). All other chemicals were commercially available products of analytical grade.

Methods

Preparation of Celecoxib solid dispersion by the Solvent evaporation method

The calculated amount of Celecoxib and the employed polymers (HP- β -CD, PVPK30 and Urea) in different drug-polymer ratios (1:2.5,

1:5, 1:7.5 and 1:10) are weighed and mixed together in a porcelain dish. The mixture was dissolved in the least amount of methanol as a common solvent. Then, the solvent was evaporated in oven at temperature 45°C till complete evaporation.

Preparation of Celecoxib Microcapsules

CXB microcapsules were prepared by the emulsion-solvent evaporation technique. The external phase was prepared by addition of (1%) Span 80 in light liquid paraffin. The polymers used (EC or CAB) were dissolved in acetone until clear solution was obtained. The required amount of the drug was then added to obtain the internal phase. The external phase was mixed with the internal phase to carry out the emulsification process. The acetone was allowed to evaporate by continuous stirring at 350 rpm and at room temperature using magnetic stirrer. The stirring was continued at room temperature until complete evaporation of the solvent, about 5 hours.

The production yield of CXB solid dispersions or microcapsules

The production yields of the prepared Celecoxib solid dispersions and microcapsules were studied, since it measures the actual weight of the prepared solid dispersion or microcapsules (drug + polymer). This value was calculated by dividing the actual yield of the solid dispersion or microcapsules produced over the theoretical yield and multiplied by 100.

The drug content of CXB solid dispersion

A specific amount of the prepared Celecoxib solid dispersion equivalent to 5 mg was dissolved in 50 ml methanol to produce stock solution (100 $\mu\text{g}/\text{ml}$). One ml of the stock solution was withdrawn and completed to 10 ml using methanol. The solution was assayed spectrophotometrically at 252 nm as mentioned above for calculating the Celecoxib content.

The drug content of CXB microcapsules

Weighted amount of microcapsules (20 mg) were dissolved in methanol using sonication for 5min. The solution was then filtered through Whatmann filter paper. The absorbance was measured after suitable dilutions with methanol solutions at 252 nm by using (methanol : water mixture) as blank.

Micromeritic properties of the CXB solid dispersions or microcapsules

The prepared solid dispersions or microcapsules were evaluated through determination of the following parameters:

Hausner Ratio

It is the ratio between bulk density and tapped density. It gives an idea about the flow characters of powder particles.

$$\text{Hausner ratio} = D_t / D_b$$

Compressibility percent

Compressibility is indirectly related to the relative flow rate, cohesiveness, and particle size of a powder. The compressibility percent of a material can be estimated as:

$$\text{Compressibility \%} = (D_t - D_b / D_t) \times 100$$

Angle of Repose

It was measured by passing the solid dispersion powder or microcapsules through a funnel which was maintained at a fixed height in all experiments. The height (h) and radius (r) of the cone were determined. The angle of repose was calculated from the following equation.

$$\tan \theta = h/r$$

In-vitro Release Study for CXB solid dispersion or microcapsules

The in-vitro release of CXB from the hard gelatin capsules filled with known amount of solid dispersions or microcapsules (equivalent to 100 mg of Celecoxib) was carried out at 37 ± 0.5 °C for 2 hr for solid

dispersion and 24 hr for microcapsules, using apparatus II. The baskets were rotated at 100 rpm. The dissolution medium was 900 ml phosphate buffer pH 7.2 containing 1% tween 80. Samples of 5ml were withdrawn and replaced with fresh medium at appropriate time intervals. The drug content in the filtered samples was measured spectrophotometrically at 254nm after suitable dilutions.

RESULTS AND DISCUSSION

Preparation of Celecoxib by solid dispersion technique using solvent-evaporation method

Twelve different formulae of Celecoxib solid dispersions were prepared by solvent-evaporation technique. Table (1) contains the suggested formulae of Celecoxib. The formed solid dispersions varied in their physical properties according to the type of polymer used and the proportions of drug to polymer. Formulae containing PVP were more viscous, sticky and more difficult to be sieved than formulae containing HP- β -CD and Urea [3].

Preparation of Celecoxib by microencapsulation technique using emulsion solvent-evaporation method

In the present work, the preparation was done by using two polymers (EC and CAB) with different drug: polymer ratio 1:2, 1:4 and 1:6, see table (2). All the prepared CXB microspheres were spherical in shape with smooth surface in case of EC but with rough surface with CAB except CXB-CAB (1:4) which was elongated with irregular surface.

Table 1: Suggested formulae of CXB [prepared by solid dispersion]

Formula	CXB (mg)	PVPK30 (mg)	Urea (mg)	HP- β -CD (mg)
CXB-HP- β -CD (1:2.5)	100			250
CXB-HP- β -CD (1:5)	100			500
CXB-HP- β -CD (1:7.5)	100			750
CXB-HP- β -CD (1:10)	100			1000
CXB-PVPK30 (1:2.5)	100	250		
CXB-PVPK30 (1:5)	100	500		
CXB-PVPK30 (1:7.5)	100	750		
CXB-PVPK30 (1:10)	100	1000		
CXB-Urea (1:2.5)	100		250	
CXB-Urea (1:5)	100		500	
CXB-Urea (1:7.5)	100		750	
CXB-Urea (1:10)	100		1000	

Table 2: Suggested formulae of CXB microcapsules

Formula	CXB (mg)	EC (mg)	CAB (mg)	Drug - polymer ratio
CXB - EC (1:2)	500	1000		(1:2)
CXB - EC (1:4)	500	2000		(1:4)
CXB - EC (1:6)	500	3000		(1:6)
CXB - CAB (1:2)	500		1000	(1:2)
CXB - CAB (1:4)	500		2000	(1:4)
CXB - CAB (1:6)	500		3000	(1:6)

Production yield of CXB solid dispersion

The values of the production yield of the 12 formulae of Celecoxib solid dispersion before sieving were ranging from 90 to 99.62 %. Table (3) shows the production yield of the prepared formulae. The obtained results were found to be in good agreement with the specifications of the official pharmacopeias [4, 5].

Formula CXB-Urea (1:7.5) gave the best value for the production yield while formula CXB-PVPK30 (1:2.5) gave the worst value.

Production yield of CXB microcapsules

Table (4) shows that the values of the production yield of CXB microcapsules in the range from 95.14% to 99.5%. The increase in the coat to core ratio and the type of employed polymers used, i.e., EC and CAB, had a different effect in the production yield of CXB microcapsules [6, 7].

Drug content of CXB solid dispersion

As shown in table (3), the drug content of different formulae ranged from 88.57mg to 102.492mg. Punitha and his colleagues found that the drug content of 1:1CXB-Urea solid dispersion was 99.25 mg and 1:5 was 98.61 mg [8].

Drug content of CXB microcapsules

Regarding the effect of the employed polymers on the amount of CXB encapsulated (drug content), it was found that the microcapsules prepared using CAB have higher percentage of the encapsulated CXB than the CXB formulae prepared using EC. This is in agreement with the work done by Ahmed and his colleagues who studied the different effect of core to coat ratio on the drug content [6]. As shown in table (4), the encapsulated amount of CXB in different formulae ranged from 90.32 \pm 0.20 mg to 98.24 \pm 0.30 mg.

Table 3: Production yield and Drug content for CXB solid dispersion

Formula	Production yield (%)	Drug Content (mg)
CXB-HP-β-CD (1:2.5)	92.86 ± 0.35	101.52 ± 0.57
CXB-HP-β-CD (1:5)	95.125 ± 0.12	102.492 ± 1.27
CXB-HP-β-CD (1:7.5)	97.65 ± 0.04	90.634 ± 1.10
CXB-HP-β-CD (1:10)	93.66 ± 0.21	92.857 ± 0.42
CXB-PVPK30 (1:2.5)	90 ± 0.02	99.2 ± 0.89
CXB-PVPK30 (1:5)	91.83 ± 0.15	96.39 ± 1.10
CXB-PVPK30 (1:7.5)	94.36 ± 0.08	98.09 ± 0.91
CXB-PVPK30 (1:10)	97.84 ± 0.13	100.95 ± 0.71
CXB-Urea (1:2.5)	98.57 ± 0.17	98.88 ± 0.8
CXB-Urea (1:5)	99.38 ± 0.14	94.3008 ± 0.15
CXB-Urea (1:7.5)	99.62 ± 0.24	96.66 ± 0.36
CXB-Urea (1:10)	99.55 ± 0.16	88.57 ± 0.9

Table 4: Production yield and Drug Content for CXB microcapsules

Formula	Production yield %	Drug Content (mg)
CXB-EC (1:2)	99.5 ± 0.02	90.64 ± 0.2
CXB-EC (1:4)	100 ± 0.07	90.32 ± 0.5
CXB-EC (1:6)	100 ± 0.1	95.87 ± 1.26
CXB-CAB (1:2)	95.14 ± 0.05	93.80 ± 1.43
CXB-CAB (1:4)	100 ± 0.4	97.92 ± 1.13
CXB-CAB (1:6)	100 ± 0.6	98.24 ± 1.23

Micromeritic properties of Celecoxib solid dispersions and microcapsules

Angle of repose (θ)

The values obtained for the angle of repose of the prepared Celecoxib solid dispersions ranged from 12.38° to 19.5°. These values indicate that all formulae have well to passable flowability.

Concerning the data obtained for the angle of repose for the prepared CXB microcapsules, it was found that CXB-CAB (1:6) showed the best value (14.26°) while formula CXB-EC (1:4) showed the worst value (20.78°).

The Hausner ratio

The value of the Hausner ratio was found to give indication about the flow properties of solid dispersion. The values less than 1.25 indicate better flowability than values more than 1.25. The accepted scale of flowability of a powder was described in USP 30 [4].

The values obtained for the Hauser ratio of the prepared Celecoxib solid dispersions ranged from 1.039 CXB-PVP (1:7.5) to 1.46 CXB-

HP-β-CD(1:10). According to the data obtained for Hausner ratio for the prepared CXB microcapsules, it was found that CXB-CAB (1:6) showed the best value (1.032) while formula CXB-EC (1:4) showed the worst value (1.2).

Compressibility %

The values between 5 and 12 show excellent flowability; the values between 12 and 16 exhibit good flowability; the values between 18 and 21 show fair passable flowability; while the values between 23 and 35 exhibit poor flowability.

The best Carr's index for CXB solid dispersion was 3.84 for CXB-PVPK30 (1:7.5), while the worst was 20 for CXB-HP-β-CD (1:2.5).

The maximum compressibility percent for the tested CXB microcapsules was 17.18% for formula CXB-EC (1:4) and the minimum one was 3.13% for formula CXB-CAB (1:6).

This was in good agreement with work done by Tiwari and his colleagues who measured the bulk and tapped densities, angle of repose, hausners ratio and compressibility index of CXB-Sorbitol solid dispersion in various proportions and found it had a good flowability [9].

In-vitro release of CXB solid dispersion and microcapsules from Hard gelatin capsule

The data obtained and calculated for this part were illustrated in figures (1-3). Pure Celecoxib yielded the slowest initial dissolution rate with only about 66.20% in 120 minutes.

The reported data for the in-vitro release of CXB-PVPK30 can be arranged in descending order as follows: CXB-PVPK30 (1:10) > CXB-PVPK30 (1:7.5) > CXB-PVPK30 (1:5) > CXB-PVPK30 (1:2.5) > CXB as shown in Fig. (1) [10]. This was in good agreement with Muralidhar who reported that the dissolution efficiency at 20 minutes found to be 62.03 and 65.14 for CXB-PVPK30 (1:2) and CXB-PVPK30 (1:4), respectively [3].

The reported data for the in-vitro release of CXB-Urea can be arranged in descending order as follows: CXB-Urea (1:10) > CXB-Urea (1:7.5) > CXB-Urea (1:5) > CXB-Urea (1:2.5) > CXB as shown in Fig. (2). As reported by Punitha and his colleagues the increase in release rate of CXB-Urea (1:1, 1:3 and 1:5) was found to be (37.86, 53.35 and 68.06) respectively. This may be due to impact of complexation and bond formation [8]. This may lead improved solubility by reducing particle size [11].

The reported data for the in-vitro release of CXB-HP-β-CD can be arranged in descending order as follows: CXB-HP-β-CD (1:10) > CXB-HP-β-CD (1:7.5) > CXB-HP-β-CD (1:5) > CXB-HP-β-CD (1:2.5) > CXB as shown in Fig. (3). Mallick and his colleagues reported that the highest potency of the carriers was due to beta cyclodextrin enhancing the dissolution rate of Nalidixic acid [12].

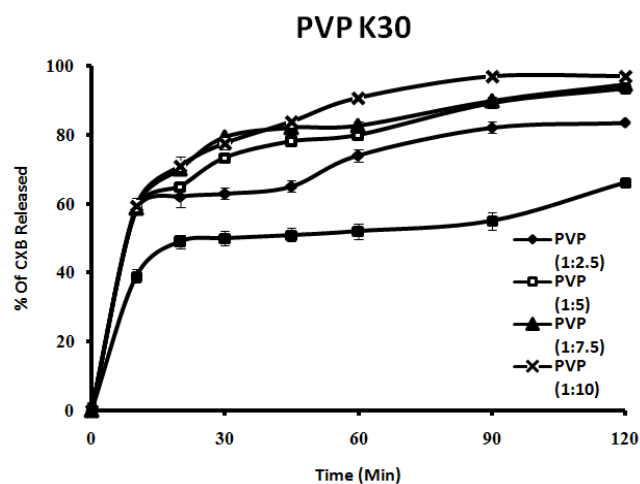


Fig. 1: The effect of PVP K30 on the in-vitro release of CXB solid dispersions using hard gelatin capsule (pure CXB + formulae 1-4)

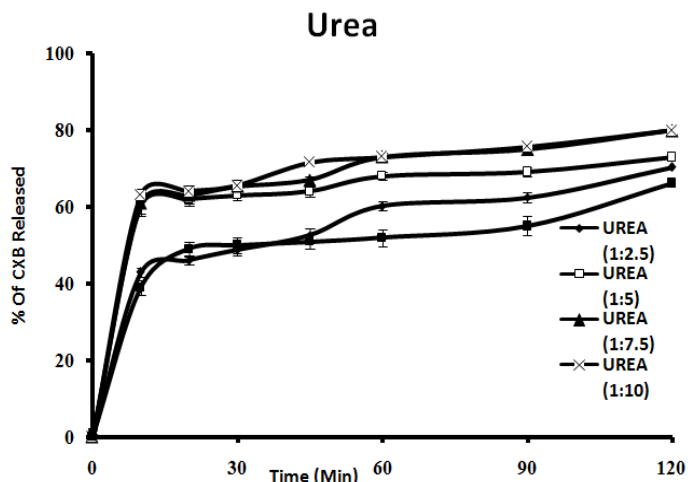


Fig. 2: The effect of Urea on the in-vitro release of CXB solid dispersions using hard gelatin capsule (pure CXB + formulae 5-8)

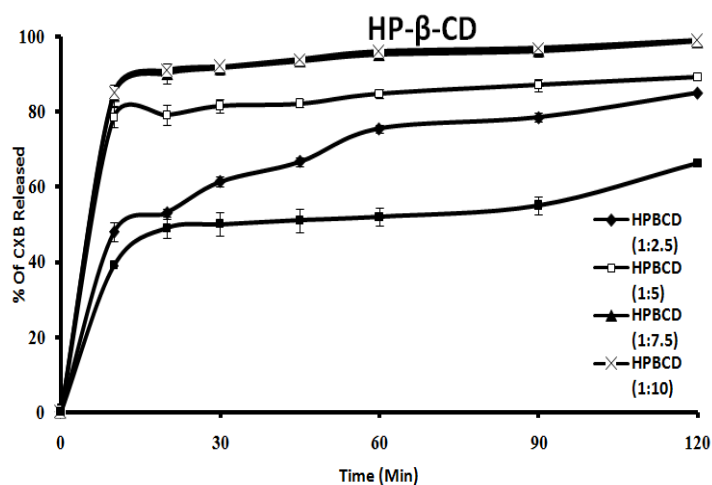


Fig. 3: The effect of HP-B-CD on the in-vitro release of CXB solid dispersions using hard gelatin capsule (pure CXB + formulae 9-12)

Fig. (4 and 5) showed the order for the in-vitro release of CXB-EC and CXB-CAB. As the coat to core ratio increased from 1:2 to 1:6 in case of EC and CAB, the in-vitro release of the drug decreased dramatically [6]. CXB formulae can be arranged according to the in-vitro release of CXB

microcapsules from hard gelatin capsules as follow: CXB-EC (1:2) > CXB-EC (1:4) > CXB-CAB (1:2) > CXB-EC (1:6) > CXB-CAB (1:4) > CXB-CAB (1:6). The results were in good agreement with the in-vitro release specifications of sustained released pharmaceutical preparations [13].

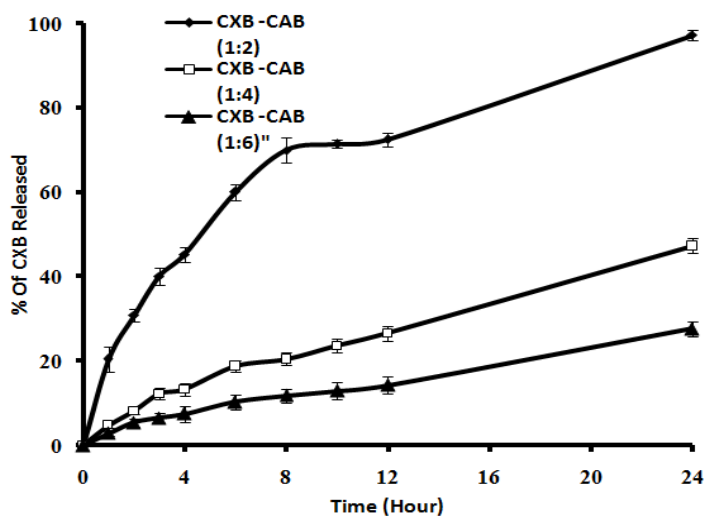


Fig. 4: In-vitro release of drug from CXB-CAB microcapsules

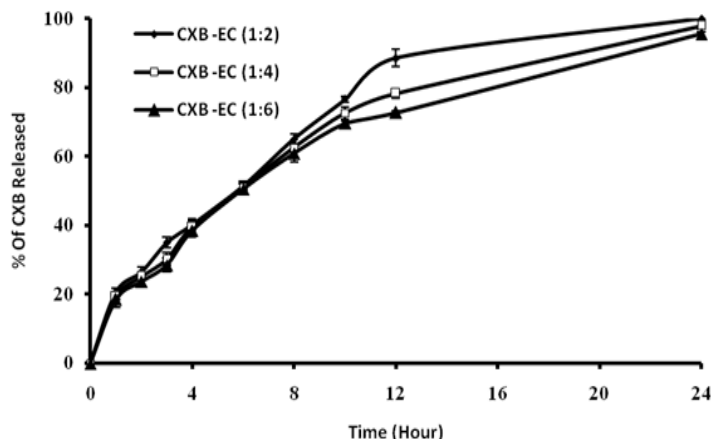


Fig. 5: In-vitro release of drug from CXB-EC microcapsules

CONCLUSION

This present study showed that when Celecoxib was dispersed in a suitable water-soluble carrier such as HP- β -CD, PVPK30 and Urea its dissolution was enhanced compared with pure drug. While when Celecoxib was combined with hydrophobic polymers such as EC and CAB sustained release is obtained. The best formula for the solid dispersion after in vitro release test was CXB-HP- β -CD (1:10), but for the microcapsules was CXB-EC (1:2).

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