Research Article

Formulation and Evaluation of Cefpodoxime Proxetil Dispersible Tablet

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ABSTRACT

Cefpodoxime proxetil (CP) is third generation cephalosporin antibiotic and has poor aqueous solubility which has direct impact on bioavailability. The aim of research work is to prepare oral dispersible tablets using solid dispersion as a core material. Solid dispersions were prepared by hot melt granulation and solvent evaporation method using varied concentrations of hydrophilic polymer (PEG 6000). Dissolution profile predicted that solid dispersion prepared with 1:4 % w/w CP and PEG 6000 by solvent evaporation has shown highest drug release. Powder blend of all formulations was evaluated for pre-compression parameters (FTIR, Hausner's ratio, Carr's index and angle of repose) and it was observed that all excipients were compatible with CP and has excellent flow properties. Dispersible tablets were prepared by direct compression method using different concentration (0, 2.5 and 5 % w/w) of croscarmellose sodium and were evaluated for drug content, weight variation, friability, dispersion time and *in vitro* drug release studies. Drug content was found to be more than 97 % for all prepared tablets whereas friability and weight variation were below 1 % and 5 % w/w respectively. Tablet formulations containing 5% w/w of croscarmellose sodium showed least dispersion time (2.51 minutes) and highest drug release 98.09 % in just 30 minutes which was better than marketed formulation (CEFOPROX) as well as pure drug. Additionally, the prepared tablets (CPGT 5%) have quick onset of action that may provide fast relief from infection and consequently improvised patient compliance.

Keywords: Cefpodoxime Proxetil, Dispersion time, Dissolution test, Fast dispersible tablets, PEG 6000, Superdisintegrant.

INTRODUCTION

Cefpodoxime Proxetil belongs to BCS class IV and is a broad spectrum Cephalosporin antibiotic mainly used in skin infection, upper respiratory tract infection and urinary tract infection. It is prodrug and gets activated in intestine by non specific esterase enzyme but due to its poor aqueous solubility which limits its absorption ultimately bioavailability (47%), it fails to reach the systemic circulation in required concentration and unable to elicit the desired pharmacological action.[1] As solubility is the primary requisite for the onset of therapeutic effect of drug by absorbing it from the absorption site. So, there is a dire need and challenge to improve the solubility of such poorly water soluble drugs. There are number of methods reported in literature for enhancement of solubility ultimately bioavailability of drug viz. particle size reduction, modification of crystal habits , drug dispersion with water soluble carriers, complexation, solubilization, etc.[2,3] Solid dispersion using water soluble carriers (e.g. PEG 6000) is one of best technique adopted for the formulation of such poorly water soluble drugs and enhances the solubility of drug by reducing the particle size or converting crystalline drug into amorphous form.[4]

As orally administered drugs completely absorb only when they show fair solubility in gastric medium and show its therapeutic effect when administered in suitable dosage form.[5] To fulfill the current medical needs, pharmaceutical technologists have developed many novel dosage forms out of them oral dispersible tablets are one of the most popular dosage form. Oral dispersible tablets are dosage forms that are placed in mouth, allowed to disperse/dissolve in the saliva without the need of water and provide a quick onset of action and immediate relief from infection.[6] Dispersible tablets achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx and oesophagus as saliva passes down. Moreover, it is convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water and hence, increased patient compliance.[7]

In this research work, solid dispersions were used as core material for the preparation of dispersible tablets. Tablets were prepared by direct compression method using different concentration (0%, 2.5% and 5%) of croscarmellose sodium (CCS) which is used as superdisintegrant. CCS rapidly swells to 4–8 times its original volume on contact with water and thus causes a burst release of drug through the polymer. Prepared tablets were evaluated for drug content, thickness, hardness, dispersion time, friability, *in vitro* drug release studies. Moreover, the optimized formulation was also compared with immediate release market formulation (CEFOPROX) in order to know the actual increase in solubility and dissolution of CP.

MATERIALS AND METHODS

Cefpodoxime proxetil (CP) was a kind gift from Redico's Remedies Baddi. PEG 6000, Magnesium stearate and Croscarmellose sodium were purchased from Qualikems Fine Chemicals Pvt. Ltd., New Delhi.

Preformulation studies

Solubility study

For determination of qualitative or crude solubility, a known amount of the drug (10 mg) was dissolved in the various solvents (water, methanol, ethanol, chloroform, PBS 1.2, PBS 6.8 and PBS 7.4). The crude solubility was observed by visual inspection.

For quantitative solubility study, excess amount of drug was taken in thoroughly cleaned volumetric flask containing 10 mL of different investigated solvents and kept in water bath shaker (Dynamik Laboratories, Mumbai) for 72 hrs at temperature of 37°C tightly closed. The solution was filtered and analyzed spectrophotometrically at 235nm.

Drug and excipients interaction

FTIR study was carried out to find out any type of interaction between drug and excipients. IR spectra of pure drug and drug with PEG 6000, MCC, Magnesium stearate and Croscarmellose sodium were studied.

Preparation of physical mixture

Drug and excipients were weighed in 1:1 % w/w ratio, uniformly mixed and passed through 40# sieve.

Preparation of treated Samples

The prepared physical mixtures were filled in transparent glass vials and covered with brown colored rubber stoppers. Vials were further wrapped with aluminum foil and placed in stability chamber under stress condition (40ºC ± 2°C / 75% RH ± 5 %RH) for 30 days. Samples were investigated on the basis of FTIR studies and visual studies on 0th day, 7th day, 15th day and 30th day.

Fourier Transform Infrared Spectrometry (FT-IR)

One part of sample was mixed with three parts of potassium bromide in a mortar and triturated. The triturated sample was placed in pellet maker and compressed using hydraulic press. The FT-IR spectrum was obtained in FT-IR spectrometer, Mode spectrum RXI, (Perkin Elmer, England) over the range 400 – 4000 cm^{-1}.[8]

Visual inspection

Visual inspection was done to check any change in color and flow of the prepared treated samples and physical mixtures, compared with pure drug.

Evaluation of powder blends of cp

The prepared blends were subjected for following pre-compression studies.

Angle of Repose (θ)

For determination of angle of repose (θ), the blend was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower.[7] Angle of repose is measured by following equation

$$\tan\theta = \frac{h}{r} \quad \ldots\ldots 1$$

Where, θ = the angle of repose, h = height of pile, r = radius of the base of pile

Bulk Density (Db)

Bulk density (g/ml) was determined by pouring bulk powder into a graduated cylinder via a large funnel and measuring the volume and weight.[7] Bulk density can be calculated by the following formula:-

$$Db = \frac{M}{Vb} \quad \ldots\ldots 2$$

Where, Db = Bulk density, M = Mass of the powder, Vb = Bulk volume of the powder

Tapped density (Dt)

Tapped density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapping apparatus, which is operated for a fixed number of taps (100) or until the powder bed volume has reached a minimum. The tapped density is computed by taking the weight of drug in cylinder and final volume.[9] It is calculated according to the following formula:-

$$Dt = \frac{M}{Vt} \quad \ldots\ldots 3$$

Where, Dt = Tapped density, M = mass of the powder, Vt = bulk volume of the powder

Compressibility Index (Carr's Consolidation Index)

The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability.[7,9] It is calculated according to the following formula:-

$$\text{Carr's index (\%)} = \frac{Dt-Db}{Dt} \times 100 \quad \ldots\ldots 4$$

Where, Dt = Tapped density of the powder, Db = Bulk density of the powder

Hausner's Ratio

Hausner's Ratio is an indirect index of ease of powder flow. If the Hausner's ratio of powder is near to 1.25, indicates better powder flow.[10] It is calculated by the following formula;

$$\text{Hausner ratio} = \frac{Dt}{Db} \quad \ldots\ldots 5$$

Where, Dt = Tapped density of the powder, Db = Bulk density of the powder

Formulation of Dispersible Tablets

Solid dispersions were prepared by hot melt granulation and solvent evaporation method using water-soluble carrier PEG 6000, in varying proportions (1:1, 1:2, 1:3 and 1:4 % w/w).

From dissolution studies it was concluded that Solid Dispersion containing 1:4 % w/w CP and PEG 6000 prepared by solvent evaporation showed highest dissolution rate and thus were selected for the preparation of dispersible tablets.

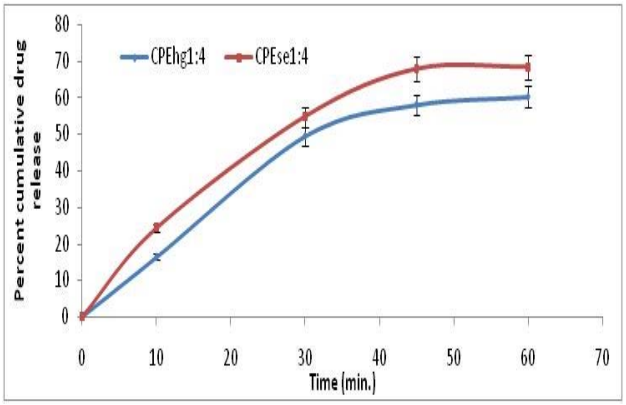

Figure 1: Percent cumulative drug release form solid dispersions (1:4 % w/w) prepared by hot melt granulation (CPEhg1:4) and solvent evaporation method (CPEse1:4)

For the preparation of dispersible tablets we have used three different concentrations (0, 2.5 and 5 % w/w) of Croscarmellose sodium (CCS) in order to know the optimum amount of disintegrant in the tablets. CCS is widely used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules.

50 tablets were prepared for each batch by direct compression method using single punch hand operated machine.

Table 1: Composition of the dispersible tablet formulation (CPGT)

Formulation code	Ingredients			
	Solid dispersion (%)	CCS (%)	Magnesium stearate (%)	MCC
CPGT0%	80	0	0.5	q.s
CPGT2.5%	80	2.5	0.5	q.s
CPGT5%	80	5	0.5	q.s

Evaluation of dispersible tablets

Drug content

Ten tablets were accurately weighed and powdered. A quantity equivalent to 100 mg of CP was dissolved in 100 ml of methanol and the contents were diluted suitably with methanol and the absorbance was measured at λ_{max} 235 nm.[6] The drug content of Cefpodoxime Proxetil was determined using the equation given below;

$$\% \text{ Assay} = \frac{Abs_T}{Abs_S} \times 100 \quad \ldots\ldots\ldots\ldots 6$$

Weight Variation

The average weight of 10 tablets was calculated and compared with the individual tablet weight.

Dispersion Time

Dispersion time was studied by dropping the tablet into 100 ml water and observed visually for complete dispersion. According to IP specifications dispersion time should not cross the limit of 3 min for dispersible tablets.[11]

Hardness

The hardness of 5 tablets of each batch (CPGT0%, CPGT2.5% and CPGT5%) was determined using Dr. Schleuniger hardness tester. The breaking strength was measured in Kg/cm^2.[9]

Thickness and Diameter

Thickness and diameter of tablets (n=5) was determined using Vernier caliper.

Friability

Friability test was carried out by using Roche friabilator (Union Sci Instruments Corp, Mumbai, India). Ten tablets were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W final). The % friability was then calculated by;

F = W initial – W final / W initial x 100 7

In vitro release study

In vitro release studies were carried out in USP type II (paddle type) apparatus using PBS ph 6.8 as dissolution medium. The temperature was maintained at 37 ± 0.5^o and the rotation speed was kept at 75 rpm. Aliquots (5 mL) of dissolution medium were withdrawn at 5, 10, 15, 20, 30, 45 minutes and equal volume of fresh medium was replaced to maintain the sink conditions.[11] The samples were then filtered using a whatman filter paper and analyzed spectrophotometrically at 235 nm. According to IP 2007, dispersible tablet should show 80% drug release within 30 min. The obtained dissolution data of all samples were fitted into the following equation;

$$C_i = A_i \left(\frac{V_s}{V_t}\right) . \sum_{i=1}^{n-1} A_i \left[\frac{V_t}{V_t - V_s}\right] \quad \ldots\ldots\ldots\ldots 8$$

Where, C_i is the corrected absorbance of ith observation, A_i is the observed specific absorbance, V_s is the sample volume, and V_t is the total volume of dissolution medium.

Where, Abs_T is the absorbance of tablet and Abs_s is the absorbance of standard stock solution.[11,12]

Kinetic Modeling

To establish a relationship between the release kinetics of the dissolution study, data obtained from *in vitro* dissolution study was fitted into various kinetic models: zero order as cumulative percent of drug dissolved *vs.* time, first order as log cumulative percentage of drug remaining *vs.* time and Higuchi's model as cumulative percent drug dissolved *vs.* square root of time. To determine the mechanism of drug release, the data were

fitted into Korsmeyer and Peppas equation as log cumulative percentage of drug released *vs.* log time, and the exponent n was calculated from slope of the straight line. For slab matrix, if exponent is 0.5, then diffusion mechanism is fickian; if 0.5<n <1.0, mechanism is non-fickian, n = 1 to Case II (relaxational) transport, and n > 1 to super case II transport.[12]

RESULTS AND DISCUSSION

Preformulation Studies

Solubility study

The results (Table 2) depicted that the drug is highly soluble in methanol & ethanol and insoluble in water & chloroform. Solubility studies were also performed in different buffer solutions to select the dissolution media which could maintain the sink conditions during *in vitro* release studies. The drug is slightly soluble in all buffers but has shown maximum solubility in PBS 6.8 (0.343 mg/ml) and was selected a dissolution medium for *in vitro* dissolution study.

Table 2: Solubility of CP in various solvents

Solvent	Solubility (mg/mL)
Water	0.11 ±0.02
Methanol	14.32±0.11
Ethanol	11.21±0.05
Chloroform	0.12±0.03
PBS 1.2	0.263±0.008
PBS 6.8	0.343±0.011
PBS 7.4	0.318±0.012

Drug excipients interaction study

FTIR spectrum (Figure 2) of CP showed a peaks at 3743 cm^{-1}, 3311 cm^{-1}, 3308 cm^{-1}, 2998 cm^{-1}, 2939 cm^{-1}, 2302 cm^{-1}, 1754 cm^{-1}, 1678 cm^{-1}, 1534 cm^{-1} & 1273 cm^{-1} were due to amide N-H stretch, alcohol/phenol O-H stretch, alkynyl C=C stretch, ketone C=O stretch, amide C=O stretch, aromatic C=C bending, C-H stretching respectively. The characteristic peaks of the drug in the IR spectrum were retained in the treated sample when compared with physical mixture which indicated that there is no incompatibility between drug, carriers and excipients. So, these excipients can further be used in the formulation.

Visual inspection

Results of treated samples revealed that there was no discoloration, liquefaction or clump formation in the prepared samples. No change in flow properties and color of drug after treating it for one month at 40ºC ± 2°C/75% RH ± 5 %RH indicating drug was physically compatible with all the excipients.

Evaluation of Powder Blends of CP

Bulk density and Tapped density

Calculated bulk density and the tapped density were found in the range of 0.48-0.52 g/ml and 0.59-0.55 g/ml respectively (Table 3), which inferred that powder is loosely packed. These values were further used for calculation carr's index and hausner ratio.

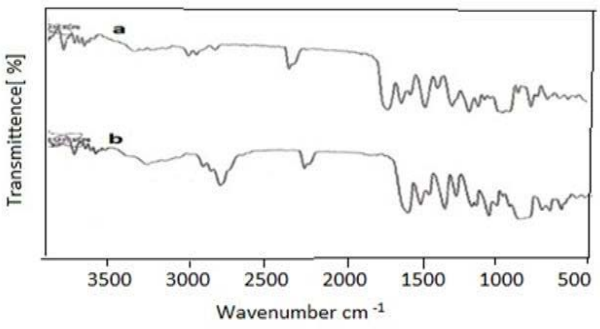

Figure 2: FTIR spectra of pure Cefpodoxime Proxetil (a) and CP with PEG 6000, MCC, Magnesium Stearate and Croscarmellose sodium (b)

Carr's Consolidation Index (Carr's index %)

The compressibility index of all the prepared formulation lies in the range of 10.34% - 12.73 % inferring the blend possessed excellent flow in all formulations.

Hausner's Ratio

The Hausner's ratio was obtained in the range of 1.12 - 1.15 revealing good flow ability.

Angle of repose

From results (Table 3) it was found angle of repose was in the range of 27.44 -29.01. Angle of repose between 25 - 30 indicate excellent flow.

Evaluation of Dispersible Tablets

Drug content

The calculated drug content (Table 4) of all the formulations determined spectrophotometrically was found to be in the range of 97.53-99.06%, under acceptable limits (85-115%). Results inferred that formulations containing 5% CCS showed highest 99.07 % drug content.

Weight Variation

Prepared tablets of all batches weighs in between 600 to 602 mg. The results showed that all formulations were within IP limits. Weight Variation results are represented in table 3. Uniformity of weight indicates equality of drug content in each tablet and hence reduced chances of dosing error.

Hardness

Tablets formulated with 0, 2.5% CCS showed 5.2 and 4.1 kg cm^{-2} hardness respectively where as tablet formulated with 5% CCS showed 3.6 kg cm^{-2} hardness. The hardness of tablets is inversely proportional to the concentration of superdisintegrant *i.e.* on increasing the concentration of superdisintegrant, the value of hardness decreases.[6,13] Hardness have direct impact on drug release as greater

the hardness lesser will be the release from polymer matrix. Formulation containing 5% w/w of CCS was considered for further studies because it showed optimum hardness that may lead to immediate drug release.

Thickness and Diameter

The diameter of tablets was observed between 12.78 mm to 12.82 mm and thickness was in the range of 5.12 mm to 5.15 mm. There was no significant difference in thickness and diameter of tablets in each batch.

Table 3: Pre-compression parameters of powder blends

Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
CPT5%	0.52±0.02	0.58±0.04	10.34±0.04	1.12±0.02	27.44±0.02
CPGT0%	0.48±0.04	0.55±0.02	12.73±0.02	1.15±0.03	29.01±0.03
CPGT2.5%	0.49±0.03	0.56±0.03	12.5±0.03	1.14±0.02	26.45±0.05
CPGT5%	0.52±0.01	0.59±0.03	11.86±0.02	1.13±0.03	27.52±0.11

Table 4: Different parameters for the dispersible tablet containing 5% CCS

Formulation code	Diameter (mm)	Thickness (mm)	Hardness (kg cm^{-2})	Weight (mg)	Dispersion time	% Friability	% Drug content
CPT5%*	12.79±0.02	5.12±0.05	3.8±0.4	600.3±2.7	2.52±0.14	0.32±0.03	97.53±0.04
CPGT0%	12.81±0.04	5.14± 0.03	5.2±0.2	598.8±3.1	4.52±0.12	0.36±0.02	98.63±0.03
CPGT2.5%	12.82±0.02	5.15± 0.03	4.1±0.3	598.8±3.1	3.42±0.13	0.31±0.02	98.87±0.02
CPGT5%	12.78±0.04	5.13± 0.02	3.6±0.2	598.8±3.1	2.51±0.11	0.50±0.03	99.07±0.03

*Dispersible tablets without solid dispersion containing 5 % CCS

Dispersion Time

The results indicated that the batches with 0 and 2.5% of CCS fail to disintegrate within acceptable limit, only the tablets with 5% CCS dispersed within 3 minutes. From results (Table 4), it was observed that dispersion time decreases with the augment of disintegrant concentration. Tablets containing 5 % CCS have optimum hardness and less dispersion time, which may be due to higher concentration of superdisintegrant that absorb water and swells, and ultimately drug is busted out within 3 minutes. Less dispersion time indicate that tablet may be dissolved in mouth rapidly and hence, laterally may show fast and quick therapeutic effect than pure drug tablet.

Friability

The friability of tablets was in the range 0.3% to 0.5% and the results are compiled in Table 4. Friability of tablets is within IP limits which indicate that formulations are suitable to bear wear and tear during transportation.

Tablet compressed with 5% w/w concentration of CCS (CPGT5%) was found to be optimum on the basis of hardness, thickness, diameter, dispersion time and friability.

***In vitro* Release Studies**

From the graph (figure 3), it was clear that CPGT0% have shown minimum release within 5 minutes compare to CPT5%, CPGT2.5% and CPGT5% which may be due to presence of CCS. The dissolution profile of CPT5% showed lowest drug release among all the prepared formulations whereas CPGT0%, CPGT2.5% and CPGT5% resulted 80.12, 84.65 and 98.09 % release in 30 minutes respectively which may ascribed due to presence of water soluble polymer (PEG 6000).

PEG 6000 increased solubility of drug by entrapping pure drug in the helical interstitial spaces of PEG molecule and also reducing the particle size.[4,14] The increase in the dissolution kinetics from polyethylene glycol soluble dispersion is also due to the reduction of crystal size, absence of aggregation of drug crystals and conversion of the drug from crystalline to amorphous/microcrystalline state.

Tablet formulations CPGT5% (containing 5% w/w CCS and solid dispersion) was found to be optimum on the basis of drug content, hardness, dispersion time and *in vitro* release so only this formulation was considered for further studies.

Kinetic Modeling

The *in vitro* release data (CPT5% and CPGT5%) was fitted into various models like Zero order, First order, Hixon Crowell, Higuchi and Korsemeyer Peppas models to know kinetics of drug release from formulations. The slope obtained 0.515 for CPGT5% was greater than 0.455 (standard value) indicating non-fickian diffusion as possible mechanism of drug release and drug is releasing by higuchi kinetis (highest R^2 value). Non-fickian drug release may be due to drug release may diffusion or erosion of the polymer. The slope obtained 0.651 for CPT5% was greater than 0.455 indicating non-fickian diffusion as possible mechanism and the value of regression coefficient indicated that the drug is releasing by First order (highest R^2 value).

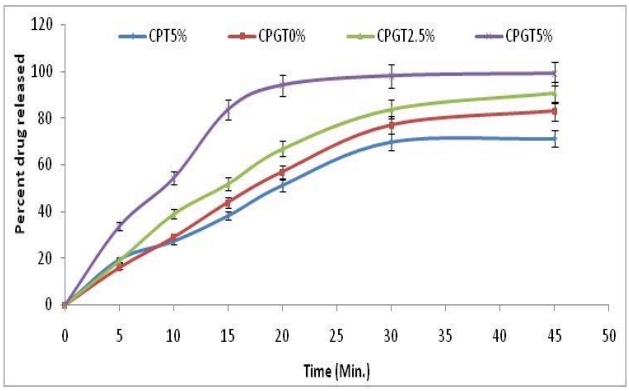

Figure 3: Percent cumulative release of Cefpodoxime Proxetil dispersible tablets

Comparison of Tablet formulation (CPGT5%) and Marketed Formulation

Dissolution studies were performed in PBS 6.8 to compare the dissolution profile of pure drug (CP), CPGT5% with market formulation (CEFOPROX). CEFOPROX is marketed as immediate release 'Uncoated dispersible tablet' formulation.

From the graph (Figure 4) it was depicted that that CP, prepared tablets (CPGT5%) and marketed formulation have shown 18.27, 84.09 % and 98.09 % release of drug in 30 minutes respectively. After 45 minutes CPGT 5% released 99.13 % drug while market formulation released only 89.13 % drug. It is clear from the results that CPGT 5% is better in dissolution and is further considered to be more bioavailable at target site. The tablets containing CPGT5% exhibited good *in vitro* disintegration and dissolution which may lead to enhanced bioavailability of the drug. Moreover the prepared tablets (CPGT5%) have additional advantages like quick onset of action, increased patient compliance and fast relief from infection.

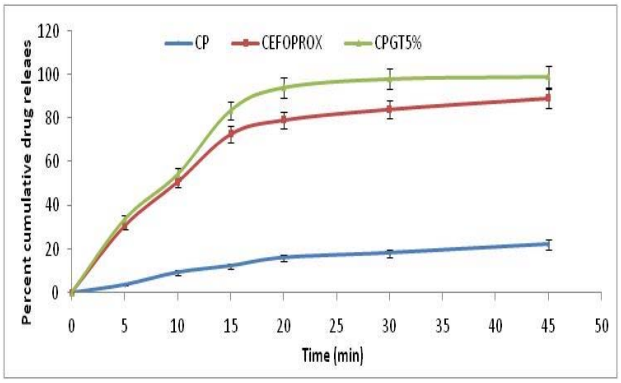

Figure 4: Dissolution profiles of pure drug (CP), CPGT 5% and CEFOPROX

CONCLUSION

Oral dispersible tablets were prepared using solid dispersion (1:4 % w/w CP and PEG 6000) as core material and CCS as superdisintegrant by direct compression method. Out of all formulations (CPGT0%, CPT5%, CPGT2.5% and CPGT5%), tablets containing 5% w/w of CCS (CPGT 5%) showed least dispersion time (2.51 minutes) and highest drug release (98.09 % in 30 minutes) as compared to marketed formulation (CEFOPROX) (84.09%) and pure drug (22.22 %). These results indicated that CPGT 5% is more efficacious than marketed formulation (CEFOPROX) and pure drug due to higher dissolution and improved solubility due to presence of water soluble polymer (in the form of solid dispersion) and superdisintegrant (CCS). Dispersible tablets CPGT5% may be a better choice of drug delivery system for Cefpodoxime proxetil (CP) since it provides quick relief from severe infection with enhanced patient compliance.

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