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Short Communication

Drug development of paracetamol derivative as antimicrobial activity

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ABSTRACT

Paracetamol derivatives with their N-subsitituted Acyclic Analogues and then subsitituted with a pro drug to enhance its activity by forming cocrystal of Antibacterial & Antifungal and then enhancing the analgesic activity of Paracetamol by attaching it to Dendrimers which enhance it activities against E. Coli & Staphylococcus Auerus and they exhibit high to moderate antimicrobial activity.

1. Introduction

Paracetamol shows two major activities that are analgesic and antipyretic, since more than 6 decades. It shows a great activity and effective medications against the pain relief and control fever in adults and children.[1] Changing or varying the substituent is common method for drug design in medicinal chemistry. We aimed to synthesize and to yield a new condensed paracetamol derivative showing us both analgesic and antipyretic effect and activity. The simple, efficient, sensitive, accurate and economical analytical techniques for quantification of such newly synthesized derivatives is needed in pharmaceutical pasture. There are various methods for determination of Acetaminophen, such as flow of injection, liquid chromatography, capillary electrophoresis, electrochemical techniques and spectrophotometric methods. Spectrophotometric is mainly done for the compounds based on nitration, oxidation, and hydrolysis to p-aminophenol followed by diazotiation and phenolic coupling.[1] Drug-Drug Cocrystals (DDC) are used for the commericial purposes. We made this approach as physician describes the combination of different drugs to get results and such combination can be converted into cocrystals and reduce the compliance of patients but will be economic as well. These techniques of cocrystals has been successful in HIV related drug, combination drug, tuberculosis, effective antibacterial drug, patient compliance, solubility, dissolution rate, bioavailability, and stability of at least one component improved through DDCs.[2] Molar ratio of the drugs are fixed so their cocrystals formation occurs according to Stoichiometric rule, but the dosage of each drug varies from the patient's age, race or ethinicity and clinical indications solid dosage forms of paracetamolcontains single-single ingredient or combination with other Non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and antispasmodic drugs. Paracetamol contains no basic or acidic sites, the exientence of H-bond acceptor (oxygen in amide) and donor (OH and NH group) makes an excellent model drug for cocrystallisation. Normally, physicians describe the antibiotics with analgesic/antipyretic drug and its practice the oral administration. Current study of (AZT-PCM) system is studied by using solvent evaporation method.[2] Dendrimers are the best class of macromolecules as their structures can be intelligently designed to improve the activity and increase selectively. These are usually

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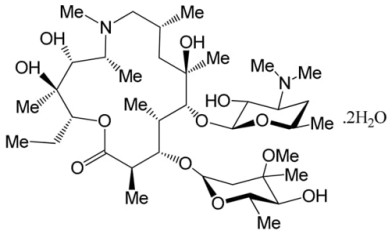
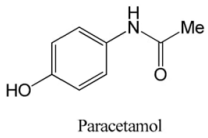
unique highly-branched 3-Dimensional macromolecules that arise from central core. These several unique properties associated with dendrimers which allow them to use in many applications such as catalysis, sensing and fluorescence applications.[3] Paracetamol will help us to reduce the morphine, thereby diminishing morphine-related opposing effects, the implicit principle is that the distinct modes of action of paracetamol and morphine provide maximum analgesia to manage and give the lower dose of morphine. Smaller dose of morphine will cause less adverse effect. So, after performing all this determination and analytical study the moiety or the product is derived.



Azithromycin dihydrate



Paracetamol

2. Selection of Active Pharamceutical Ingredient

Azithromycin (AZT) is found in three forms in solid state i.e., Anhydrous form, Monohydrate, Dihydrate. The Dihydrated form is the most stable form between these two hydrated forms. It is very poorly water-soluble drug but when it is prepared in solid form it shows the enhanced solubility and dissolution. Azithromycin dehydrate bioavailability is 37% if given by oral route. Major advantage of azithromycin is that its absorption is not affected by the food. Macrolides inhibits the growth of bacteria by inhibiting the protein synthesis of ribosome and translation.

In order to replicate, the bacteria need or require a specific kind of protein synthesis which is done by the ribosomal protein. AZT it binds to the 23S rRNA of bacterial 50S ribosomal subunit. AZT stops the bacterial protein synthesis by inhibiting the protein synthesis by translocation and inhibiting the assembly of 50S ribosomal subunit. AZT is stable at the low pH and its longer half-life increases its concentrations in the tissues.

Paracetamol shows both the antipyretic as well as the analgesic activity. Acteaminophen shows the occurrences of the allergic reactions. Its oral bioavailability is 88% and it reaches its maximum plasma concentration within 90minutes after the ingestion.[4] Paracetamol gets easily metabolize to p-acetaminophen and it easily crosses the BBB and converted into the AM404 because of the FAAH. Acetaminophen is excreted by mainly through urine and 90% of the administered drug is excreted within next 24hours of the ingestion.

So the combination of these API shows the synergism and it gives an analgesic as well as the antibacterial effect. The paracetamol will selectively inhibit the effect of COX-2 in the spinal cord and due to which the transmission of pain impulses to higher centres is inhibited. AZT with its cocrystals helps to show the Antibacterial and Analgesic activity at the time. And it helps to cure the symptoms as well as the infection.

3. Experimental Section

1. **Synthesis of 2-Paracetamolylacetylpyrazolidine-3,5 -dione**: Paracetamolacetic acid hydrazide, diethylmalonate, triethylamine and dioxane were added in each other and this mixture was refluxed for further 70h. The reaction the later checked by performing the TLC. The refluxed mixture was then poured on the ice and the precipitate was filtered and recrystallized by the ethanol and powder was yield in 79%. And melting point was determined as 220-222 degree Celsius.[1]
2. **Synthesis of Cocrystals :** Granules of Paracetamol and Azithromycin dehydrate were added in the solvent i.e. water/methanol (1:1 v/v). Then these mixture was sonicated for the next 10minutes and the temperature of 40 degree celsius and kept under the dark for few days until the crystals are formed. These were stored in dark as the precautionary measure.[2]
3. **Synthesis of Paracetamol-Terminal Dendrimer (Fourth-Generation D11):** The dendrimer D11 is prepared by the procedure analogous to the synthesis of D2, dendrimer D11 from the dendrimer D10, acetaminophen 2, K2CO3 in 7ml DMF. The yielded product was the yellow powder.[3]

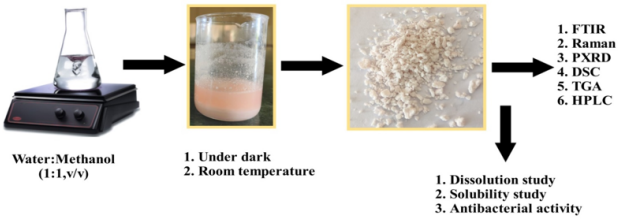


Figure 1:

3.1. Analytical studies

1. *FTIR Spectroscopy:* The FTIR analysis has been a valuable and extensively used tool for characterization and identification of new solid forms, in addition to other spectroscopic techniques. The FTIR spectra of raw drugs, physical mixture and cocrystal were obtained for possible interaction and chemical

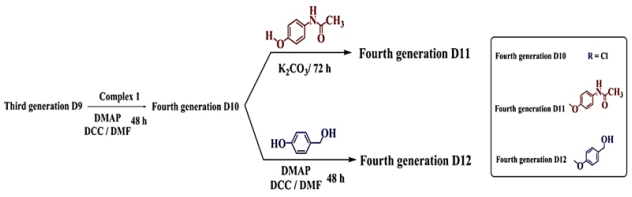


Figure 2:

compatibility.

2. *Raman Spectroscopy:* Raman experimental results indicated that the crystalline phase of the cocrystal is not a simple combination of starting materials, but a different crystal phase due to hydrogen bonding interactions between AZT and PCM. Therefore, from Raman analysis it is further confirmed that AZT-PCM afford cocrystals as a result of non-covalent interactions.
3. *PXRD Characterization:* Conversely, PXRD is a readily available technique generally used for confirmation and determination of bulk purity and crystallinity of the bulk material
4. *UV Spectroscopy:* Performing the uv spectroscopy to measure the light absorbance property of the drug and to study and analyse the chemical properties of a material. AZT wavelength is 199.2nm and PCM is 243.90nm.
5. *DSC Analysis:* DSC Analyses are extensively utilized for cocrystals confirmation. In these we study of biochemical reactions, to measure thermodynamic of solids or liquids phase transitions and differential scanning calorimetry.
6. T*hermogravimetric Analysis:* TGA is performed to analysis and to determine selected characteristics of materials that exhibit either mass loss or gain due to decomposition oxidation, or loss of volatiles.
7. *HPLC Analysis:* Performing this analytical study was done to determine the qualitative and quantitative analysis of the component to confirm the identity of drug.
8. *Powder Dissolution Study:* Drug release study of the cocrystals and its dissolution rate is determined in this study to check its bioavailability.
9. *Microbial Assay:* The comparative zone of inhibition and MIC studies of the selected antibiotic and cocrystal were performed against Escherichia coli (E. coli), Salmonella typhi (S. typhi) and Klebsiella pneumonia (K. pneumonia) bacterial strains is going to be studied.[5–9]

4. Conclusion

After carrying out the whole experiment we conclude that our paracetamol derivative moiety can show an

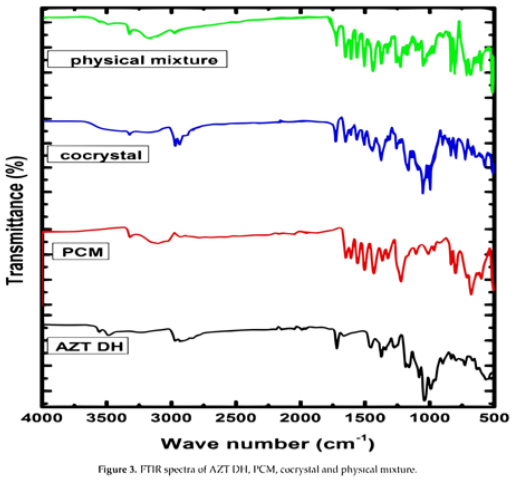


Figure 3. FTIR spectra of AZT DH, PCM, cocrystal and physical mixture.

Figure 3:

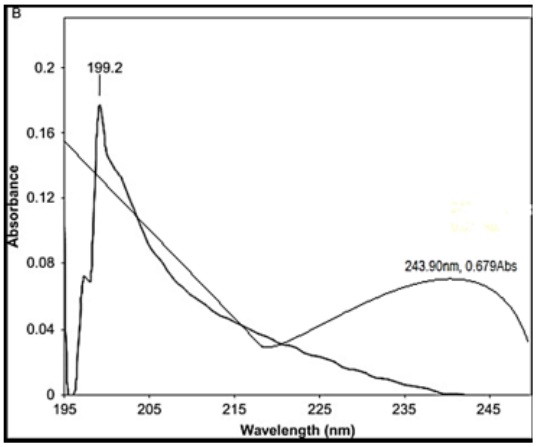


Figure 4:

Table 1:

Bacterial	Sample Amount(μg)	AZT DH (100%) Zone of Inhibition (mm)	Cocrystal (83%) Zone of Inhibition (mm)
K. pneumonia	5	21±0.45	23±0.41**
	2.5	17±0.40	18±0.37*
	1.25	14±0.35	15±0.30**
	0.62	10±0.25	12±0.23***
E. coli	5	15±0.32	16±0.27*
	2.5	10±0.30	12±0.25***
	1.25	8±0.25	9±0.27**
	0.625	-	-
S. typhi	2.5	9±0.30	10±0.27**
	1.25	7±0.24	7±0.21*
	0.62	-	-

optimal antimicrobial activity with an Analgesic effect too. The product gives an prolong analgesic activity and antimicrobial activity with reduced dose.

5. Source of Funding

None.

6. Conflict of Interest

None.

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