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CYCLODEXTRIN/ACYCLOVIR COMPLEXATION FOR IMPROVED DRUG DELIVERY

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ABSTRACT

Introduction-Pharmaceutical adjuvants known as cyclodextrins are widely used. These adjuvants' chemical structure can interact with drug molecules of the proper size to produce an inclusion complex. The main goal of the previous development of such complexes was to make drug more soluble in water. Instead, the focus of the current study is on enhancing the permeability of guest molecule from BCS class III, and the solubility of the complex was also examined as a result of using poloxamer (Pluronic F 108). **Method**-Acyclovir was chosen as the guest molecule and Hydroxypropyl Beta Cyclodextrin (HPβ-CD) and Randomly Methylated Beta Cyclodextrin (RMβ-CD) as the host molecules, respectively, for the production of host-guest inclusion complexes. Pluronic F 108 was taken as a surfactant. **Result**-The absorption and scattering properties of prepared complexes were analyzed by UV Spectroscopy and it was found that the rate of agglomeration of complexes was directly proportional to the concentration of Cyclodextrin added which concluded that the permeability of the drug enhanced on complexation with cyclodextrin and further enhancement was observed with addition of Pluronic F 108.

Keywords: Cyclodextrin, Acyclovir, Inclusion complex, Permeability, Pluronic F108

INTRODUCTION

Acyclovir, also known as 2-Amino-1,9-dihydro-9-((2-hydroxyethoxy) methyl)-3H-purine-6-on), is an antiviral medication that falls under BCS class III. [29] Herpes simplex and varicella zoster, among other illnesses, are known to be treated with this drug most

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frequently. The solubility and half-life of pharmaceuticals are two of the most frequent problems encountered during their manufacture, and acyclovir is no exception due to its poor solubility and brief half-life.[12] Because of several of its benefits, oral medication is thought to be the most successful treatment out of all others. Low bioavailability presents difficulties for oral medicine delivery because it necessitates frequent dosage. [18] Acyclovir is changed into acyclovir monophosphate by viral thymidine kinase, which is then changed into acyclovir triphosphate (ACV-TP) by host cell kinase. The HSV-specific DNA polymerase is then competitively inhibited and rendered inactive by ACT, inhibiting the production of more viral DNA without impairing normal cellular functions. The prototypical antiviral drug, acyclovir, is a synthetic deoxy guanosine analogue that is activated by viral thymidine kinase. Because of its affinity for the thymidine kinase enzyme encoded by HSV and VZV, acyclovir has a selective activity. [26]

Acyclovir side effects include: nausea, vomiting, diarrhea, fatigue, headache, fluid retention, muscle or joint pain, changes in vision, hair loss, confusion, changes in behavior, yellowing of the skin or eyes, unusual bleeding or bruising, seizures, hallucinations, shakiness or numbness, and confusion.[30]

In the current investigation, we make complexes of acyclovir with cyclodextrin using a hydrophilic excipient. The hydrophilic excipient used is Pluronic F 108 also known as poloxamer. Its Chemical name is α-hydro-ω-hyroxypoly (oxyethylene) poly (oxypropylene) (oxyethylene) block polymer and Mol. Formula: $C_5H_{10}O_2$, it is a white, free flowing, prilled granules or as a cast solid, odourless and tasteless. [22] Cyclodextrins are cyclic oligosaccharides with a bucket-like form. They contain (a-1-4)-linked α-D glucopyranose units. A lipophilic core is surrounded by a hydrophilic exterior in cyclodextrin. In the pharmaceutical sectors, they are frequently referred to as "molecular cages." The discovery of cyclodextrins by Villers in 1891 and the discovery of their cyclic character by Schardinger in 1903 [9,24] laid the groundwork for the compound. Cyclodextrins are cyclic carbohydrates that are produced as a result of the bacterial breakdown of starch by the CD glycosyltransferase enzyme (bacillus macerans). Cyclodextrins are also known as cycloamyloses, cyclomaltoses, and schadinger dextrin.[25] Cyclodextrins have a number of benefits, including the ability to increase solubility, increase bioavailability, improve stabilization, lessen irritation, avoid incompatibility, modify chemical reactivity to the host molecule, act as a catalyst, stop microbial degradation, and better stabilize drugs that are sensitive to light or oxygen. There are three parent cyclodextrins: α-, β-, and γ - (which have more derivatives; in this instance, we utilize HPCD and RMCD).[3] Among these, β-cyclodextrin is economical, pragmatic, and accessible. There are two primary crystal packings in which cyclodextrins crystallise, with the first being a "round" structure with glucopyranose units in the $^4C_1$ chain conformation and the second being an antiparallel

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double helix as shown by linear maltohexaoses [7]. Further cyclodextrin derivatives can be made through aminations, esterification, or etherification. Depending on the substituent, derivative cyclodextrins may not solubilize as well as their parent cyclodextrin. The hydrophobic cavity volume of all derivatives might change, which usually serves to increase solubility, stability against light or oxygen, and help regulate the chemical activity of guest molecules. They serve as building materials. [6] A regioselective method has been used to attach up to 20 substituents to β-cyclodextrin. They are used as building blocks for the formation of supramolecular complexes based on their ability to bond covalently or non-covalently, mostly to other cyclodextrins. Another crucial characteristic is their capacity to form inclusion complexes with host molecules, which opens up the possibility of constructing supramolecular threads. [15] Metal complexes, inclusion complexes, and molecular complexes are some of the forms of complexes. The classification of complexes may be unpredictable, but it mostly depends on the types of interactions or the chemicals involved. A nonbonded entity with a clearly defined stoichiometry is the end product of the complexation process. Weak bonds like London forces, hydrogen bonds, and hydrophobic interactions are what the complexation depends on or includes. A complex formation increases drug solubility. [23] One of the most significant attributes of the cyclodextrin would be its ability of forming the inclusion complexes. Compound which can form inclusion complex with these cyclodextrin can either be solid, liquid or in gaseous state. Cyclodextrin would act as a host molecule in these inclusion complexes where the guest molecule could fit in its cavity. There should be a dimensional fit of the host as well as the guest molecule so that its out of the spectrum of breakage or formation. This binding is not a permanent state and could separate. The major element of this system would be release of the enthalpy opulent water molecule from the cavity so that the inclusion complex may form. [14] With water being the most common choice for the solvent, the state of the complex may either be solution or crystalline. The significant aid that the inclusion complex provide is being able to enhance the physiochemical properties of the host molecule while in the cavity of cyclodextrin by altering the host molecule. Unpalatability, obnoxious odour, flavor, sublimation control, volatility, stability, solubility etc. are some of the properties which can be enhanced by this system. [13] There is more than one discipline in which cyclodextrin finds its pertinence some of which are cosmetics, environment protection, food, pharmaceuticals, bioconversion, packing and textile industries. There are limitless options which are viable as guest molecules for formation of inclusion complexes with cyclodextrin some of which are straight or branched chain aliphatic, aldehydes, ketones, alcohols, organic acids, fatty acids, aromatics, gases; polar compounds like halogens, oxyacids and amines. The two basic elements that can be considered significant for the formation of these complexes are steric and thermodynamics interaction, steric interaction depends on size of host as well as the guest molecule whereas thermodynamic interaction on different

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components of the system. There is a need of net energetic driving force that is advantageous to pull the guest molecule in the cavity which is important for complex formation [27] All parent cyclodextrins have the same cyclodextrin cavity height, however the internal diameter of the cavity may vary depending on the glucose unit. Cyclic oligosaccharides with 6, 7, or 8 glucopyranose units are referred to as CDs and go by the abbreviations α-, β-, or γ-CD, respectively. Every glucose unit contains two secondary alcohols at C-2 and C-3, and a primary alcohol at C-6 with 18 to 24 sites for chemical modification and derivatization. Since solubility and dissolution are rate-limiting processes, the improvement in solubility, stability, pace, and extent of drug dissolution is seen with the sequestration of hydrophobic medicines inside the cavity of CD. Drugs that are insoluble and challenging to formulate with conventional excipients can be made simple with CDs. [4] There are numerous CD derivatives with a wide range of attributes. It is crucial to take into account their quantitative characteristics, which are quite significant in evaluation. Combining hydrophobic medication with CDs to form inclusion complexes is described quantitatively in (eq) below by an association or stability constant (ka:b)

$$K_{a:b} = \frac{[drug_a\ CD_b]}{[drug]^a[CD]^b}$$

where the sequestered drug molecule's molar ratio to the CD is represented by the letters a and b. To compare the binding efficiency of several CDs, the association constant can be useful. [16] The purpose of present study is preparation of cyclodextrin complex with acyclovir and studying the effect of hydrophilic excipient on cyclodextrin complexation and to observe the performance of cyclodextrin complexes in drug delivery Pluronic F 108 is the hydrophilic excipient we utilize in this study.

METHODOLOGY AND EVALUATION

MATERIAL

Acyclovir was given to us as a sample by Panacea Biotech LTD. Purchases of HPβ-CD, RMβ-CD, and Pluronic F108 were made from CDH, TCI, and Sigma Aldrich, respectively.

PREPARATION OF FORMULATION: Acyclovir and β-CD (HPβCD, RMβCD) complex were prepared in (1:2) and (1:3) with and without hydrophilic excipient (table:1). Acyclovir CD complex were prepared by weighing equimolar concentration of acyclovir and CD (HPβCD, RMβCD) Pluronic F108 was 2% of total amount drug and CD combined. The weighed amount of drug, CD (and Pluronic in case of complex with hydrophilic excipients) were taken in a conical flask and distilled water (which was taken as a solvent) was added to

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it. This solution was put on a flask shaker for 4 consecutive days. After removal of solution from shaker after 4 days it was filtered using simple filter paper. The filtered solution was put in a refrigerator for 1 hour and then transferred to the freeze dryer until a solid complex was formed. After the complex was formed it was removed from the conical flask and used for further evaluations [5,10].

Solubility: In this pre-formulation investigation, a suitable solvent was chosen in order to assess the drug sample's solubility and make it dissolve in it. It was determined using the flask shaking method, and a UV Spectrophotometer was used to examine the results. four conical flasks were taken. 45mg of acyclovir was added to each of the conical flask. Added 10 ml of distilled water to each conical flask. Amount of cyclodextrin derivatives added in each flask were in ratio of (1:1, 1:2, 1:4, 1:6). Kept the flasks on flask shaker for 30 hrs. filtered out all samples through Whatman filter paper. Taken 1ml of sample of filtrate and diluted up to 20ml with distill water. Scanned all the samples through UV Visible spectrophotometer [8]

FTIR analysis: To determine whether the drug is compatible with other excipients, each sample was scanned in the 400–4000 cm-1 wavelength range. The drug was scanned using FTIR both on its own and in combination with other excipients. The fine powder sample (20 mg) was evenly distributed over the ATR crystal, and the "anvil" was placed over the sample for analysis by twisting the knob in a clockwise direction and pressing "Anvil" [11,21].

X-Ray Diffractometry (X-RD): Drug and excipient X-Ray powder diffractometry was performed utilizing X-Ray diffractometry. Sample cuvettes were loaded with the necessary amount of the samples, which were then packed securely to be scanned at 20 different values between 5 and 50 degrees. Each individual sample's diffractogram was examined for crystallinity [19].

Scanning electron microscopy: 2okv strength by gold coating technique was used to conduct SEM of the produced complex using SEM EVO 40 EP, ZEISS LTD, USA. SEM analysis was done at the H.N.B. Garhwal University's USIC department of instrumentation in Srinagar (Garhwal) [20].

In-vitro studies: Permeation was done in order to access the complex for in vitro research. In order to conduct this study, utilized Franz diffusion cells. The donor compartment received a drug solution, whereas the receptor compartment received a pH 7.4 phosphate buffer solution. Between the donor compartment and the receptor compartment was a cellophane membrane. Magnetic stirrer was used on which the receptor compartment was mounted and contained magnetic beads. To keep the temperature constant, distilled water that has been preheated to 37°C is continually fed into the receptor compartment jacket. For eight hours,

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samples were removed and replaced with Phosphate Buffer Solution at predetermined intervals. A UV-Visible spectrophotometer was then used to determine the presence of drugs in all of the samples.

RESULTS AND DISCUSSIONS

Solubility: Following results were obtained on analyzing the phase solubility of the drug. From the phase solubility analysis which can be observed from the graph (fig:1). it was observed that RMβCD showed best results.

Drug content: Analyzed the drug release by calculating the drug content by using distill water at 253nm. The drug content of formulation AH2 (62.104%) and ARP2 (53.4%) were highest and lowest in AHP3. This may be because of the higher interaction sites provided by the host (HPβCD and RmβCD) molecule to the guest (acyclovir) molecule, there may be less interlinking between cyclodextrin molecules leading to strong interaction and increased drug content in the above-mentioned formulations [1,2].

FTIR analysis: FTIR analysis was done in order to check the compatibility of drug and the excipients alone as well as in combination. Compared the procured drug sample with standard spectrum of the pure drug for drug identification.

It was observed IR spectrum of Acyclovir showed absorption peak at 3227 cm^{-1},3197 cm^{-1} denoting OH stretching. The absorption peak at 2959cm^{-1}, 2992 cm^{-1}, 2918cm^{-1} due to NH stretching. The peak at 1633cm^{-1} is due to the c=o stretching

IR spectra of RmβCD showed absorption peak at 3193 cm^{-1},3212 cm^{-1},1086cm^{-1} showing OH stretching and C-O stretching. Pluronic showed peak at 3316cm^{-1},3272cm^{-1} also showing OH stretching whereas HPβCD showed peaks at 3175cm^{-1},1983cm^{-1} showing OH stretching and CH bending.As per the observation from FTIR spectra that in APH3 peak at 3677cm^{-1},2907cm^{-1} showed OH stretching, 2988cm^{-1} showed NH stretching and 1454cm^{-1} showed CH bending; in AHP2 3417cm^{-1},3439cm^{-1},3469cm^{-1}, 3201cm^{-1} showed OH stretching and at 1067cm^{-1} C-O stretching ; in APR2 2929cm^{-1},3372cm^{-1},3305cm^{-1} showed NH stretching and peak at 3390cm^{-1} showed OH stretching; in APR3 3406cm^{-1} showed OH stretching, at 3353cm^{-1} showed NH stretching and at 762cm^{-1}showed CH bending. The lack of significant alterations or shifting in drug peak heights suggests that there is no chemical interaction between pharmaceuticals and physical combinations of polymers. It was determined that, despite compositional variations, the drug is present but free from in all formulations regardless of compositional variation.IR spectra of physical mixtures of drug and excipients they don't have any chemical interactions. From the analysis it was observed that they are compatible with each other (as shown in table:2)

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Scanning electron microscopy (SEM): the formulations that were prepared were analyzed by SEM for study of the particle size, shape, surface morphology and appearance

From SEM analysis it was revealed that all formulations were rough and irregular with the exception of AH3 and ARP2 which were irregular but smooth. The complex with small particle size had better release as compared to larger ones. (As shown in table: 3)

X-Ray Diffractometry (XRD): XRD analyze that whether the complexes were amorphous in nature or not. XRD patterns recorded obtained are in the graph below. The major peaks are observed to see the nature.It was observed from the diffractogram that drug is crystalline in nature (as shown in fig.2). As sharp peaks were obtained in case of pure drug therefore drug was crystalline in nature as compared to the formulation in which intense peaks were obtained. This showed the amorphous nature of the complex.

In-vitro studies: Following results were obtained from the permeation studies performed for 8 hours using buffer of pH 7.4. It was found that the permeation of formulation APR3 was highest at 77% in 480 minutes and lowest in AH3 54% in 480 minutes. (As shown in fig.3)

CONCLUSION

In order to increase solubility and permeability and improve drug delivery, the complexes were synthesized and tested. The drug's permeability and solubility were discovered to be enhanced in an inclusion complex with HPCD, although it was discovered that the hydrophilic excipients produced the best results (table :4)

AUTHOR CONTRIBUTIONS

All authors agreed to submit the article to the current journal, offered final permission of the version to be published, made significant contributions to concept and design, data collection, analysis, and interpretation, participated in its writing and critically revised it for important intellectual content, and agreed to be responsible for all aspects of the work. According to the qualifications and rules established by the International Committee of Medical Journal Editors (ICMJE), all authors are qualified to serve as authors.

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REFERENCES

1. Abuzar SM, Hyun SM, Kim JH, Park HJ, Kim MS, Park JS, Hwang SJ. Enhancing the solubility and bioavailability of poorly water-soluble drugs using supercritical antisolvent (SAS) process. International journal of pharmaceutics. 2018 Mar 1;538(1-2):1-3.
2. Adamska K, Voelkel A, Héberger K. Selection of solubility parameters for characterization of pharmaceutical excipients. Journal of Chromatography A. 2007 Nov 9;1171(1-2):90-7.
3. Braga SS, Barbosa JS, Santos NE, El-Saleh F, Paz FA. Cyclodextrins in antiviral therapeutics and vaccines. Pharmaceutics. 2021 Mar 19;13(3):409.
4. Bíró T, Horvát G, Budai-Szűcs M, Csányi E, Urbán E, Facskó A, Szabó-Révész P, Csóka I, Aigner Z. Development of prednisolone-containing eye drop formulations by cyclodextrin complexation and antimicrobial, mucoadhesive biopolymer. Drug Design, Development and Therapy. 2018 Aug 15:2529-37.
5. Burckbuchler V, Kjøniksen AL, Galant C, Lund R, Amiel C, Knudsen KD, Nyström B. Rheological and structural characterization of the interactions between cyclodextrin compounds and hydrophobically modified alginate. Biomacromolecules. 2006 Jun 12;7(6):1871-8
6. Clercq S, Temelli F, Badens E. In-Depth Study of Cyclodextrin Complexation with Carotenoids toward the Formation of Enhanced Delivery Systems. Molecular Pharmaceutics. 2021 Mar 3;18(4):1720-9.
7. Carneiro SB, Costa Duarte FÍ, Heimfarth L, Siqueira Quintans JD, Quintans-Júnior LJ, Veiga Júnior VF, Neves de Lima ÁA. Cyclodextrin–drug inclusion complexes: In vivo and in vitro approaches. International journal of molecular sciences. 2019 Feb 2;20(3):642.
8. Cavalli R, Donalisio M, Civra A, Ferruti P, Ranucci E, Trotta F, Lembo D. Enhanced antiviral activity of Acyclovir loaded into β-cyclodextrin-poly (4-acryloylmorpholine) conjugate nanoparticles. Journal of controlled release. 2009 Jul 20;137(2):116-22.
9. Del Valle EM. Cyclodextrins and their uses: a review. Process biochemistry. 2004 May 31;39(9):1033-46.
10. Hadian Z, Maleki M, Abdi K, Atyabi F, Mohammadi A, Khaksar R. Preparation and characterization of nanoparticle β-cyclodextrin: Geraniol inclusion complexes. Iranian journal of pharmaceutical research: IJPR. 2018;17(1):39.
11. Jafar M, Alshaer FI, Adrees FA. Cyclodextrin ternary inclusion complexation: A strategy to improve solubility of poorly soluble drugs. Int. J. Pharm. Phytopharm. Res (eIJPPR). 2018 Dec 1;8(6):8-17.
12. Jambhekar SS, Breen P. Cyclodextrins in pharmaceutical formulations II: solubilization, binding constant, and complexation efficiency. Drug discovery today. 2016 Feb 1;21(2):363-8.

ISSN 2515-8260 Volume 10, Issue 05, 2023

13. Jin ZY. Cyclodextrin chemistry: Preparation and application. World Scientific; 2013.
14. Jambhekar SS, Breen P. Cyclodextrins in pharmaceutical formulations I: Structure and physicochemical properties, formation of complexes, and types of complex. Drug discovery today. 2016 Feb 1;21(2):356-62.
15. Koester LS, Guterres SS, Le Roch M, Eifler-Lima VL, Zuanazzi JA, Bassani VL. Ofloxacin/β-cyclodextrin complexation. Drug development and industrial pharmacy. 2001 Jan 1;27(6):533-40.
16. Li J, Yang M, Xu WR. Enhanced oral bioavailability of fluvastatin by using nanosuspensions containing cyclodextrin. Drug Design, Development and Therapy. 2018 Oct 23:3491-9.
17. Maher M, Pandey M, Adhikari L, Semalty A, Semalty M. Effect of hydrophilic excipients on cyclodextrin complexes of acyclovir in improving solubility, dissolution and permeability. Letters in Drug Design & Discovery. 2016 Oct 1;13(8):771-80.
18. Nair AB, Attimarad M, Al-Dhubiab BE, Wadhwa J, Harsha S, Ahmed M. Enhanced oral bioavailability of acyclovir by inclusion complex using hydroxypropyl-β-cyclodextrin. Drug delivery. 2014 Nov 1;21(7):540-7.
19. Namazi H, Hamrahloo YT. Novel PH sensitive nanocarrier agents based on citric acid dendrimers containing conjugated β-cyclodextrins. Advanced pharmaceutical bulletin. 2011 Jun;1(1):40.
20. Nicolazzi C, Abdou S, Collomb J, Marsura A, Finance C. Effect of the complexation with cyclodextrins on the in vitro antiviral activity of ganciclovir against human cytomegalovirus. Bioorganic & medicinal chemistry. 2001 Feb 1;9(2):275-82.
21. O'Mahony AM, Ogier J, Darcy R, Cryan JF, O'Driscoll CM. Cationic and PEGylated amphiphilic cyclodextrins: co-formulation opportunities for neuronal siRNA delivery. PloS one. 2013 Jun 21;8(6): e66413.
22. Rowe and Sheskey et al(2009). *Handbook of pharmaceutical excipients*. Libros Digitales-Pharmaceutical Press.
23. Saha S, Roy A, Roy K, Roy MN. Study to explore the mechanism to form inclusion complexes of β-cyclodextrin with vitamin molecules. Scientific reports. 2016 Oct 20;6(1):1-2.
24. Szejtli J. Introduction and general overview of cyclodextrin chemistry. Chemical reviews. 1998 Jul 30;98(5):1743-54.
25. Stella VJ, Rajewski RA. Cyclodextrins: their future in drug formulation and delivery. Pharmaceutical research. 1997 May;14:556-67.
26. Tripathi KD. Essentials of medical pharmacology, 7th edition. Jaypee Brothers Medical Publishers 2008; 798-800.
27. The United States Pharmacopiea. The National formulary. Available from: https://search.library.wisc.edu/catalog/999509774402121.

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28. Wang W, Zhao Q, Zhang Q. Acyclovir Combined with Naloxone in the Treatment of Viral Encephalitis: A Meta-Analysis. Journal of Healthcare Engineering. 2022 Apr 1;2022.
29. https://www.drugbank.ca
30. https://pubchem.ncbi.nlm.nih.gov

Formulations	**Coding**
Acyclovir-HpβCD complex (1:2)	AH2
Acyclovir-HpβCD complex (1:3)	AH3
Acyclovir-HpβCD complex with Pluronic (1:2)	AHP2
Acyclovir-HpβCD complex with Pluronic (1:3)	AHP3
Acyclovir-RmβCD complex with Pluronic (1:2)	ARP2
Acyclovir- RmβCD complex with Pluronic (1:3)	ARP3

Table:1 Formulation's coding

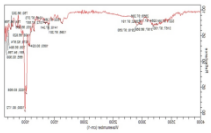
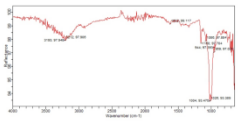
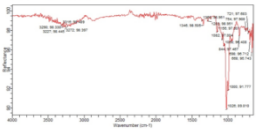
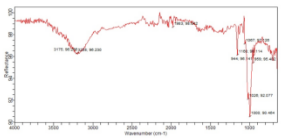
Fig.7 FTIR spectrum of acyclovir	**Fig. 8 FTIR spectra of RmβCD**	**Fig.9 FTIR spectra of Pluronic**	**Fig.10 FTIR spectra for HpβCD**
			

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Fig.11 FTIR spectra for AHP3	Fig.12 FTIR spectra for AHP2	Fig.13 FTIR spectra of APR2	Fig.14 FTIR spectra of APR3

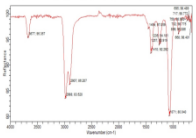
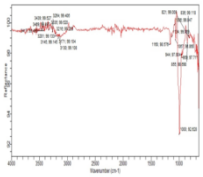
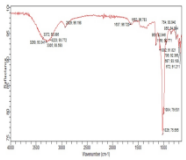
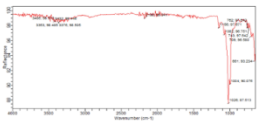

			

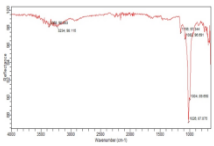
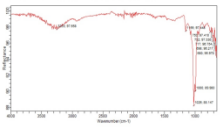
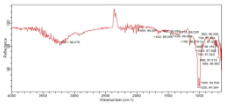
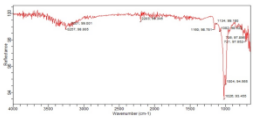
Fig.15 FTIR spectra of PARP2	**Fig.16 FTIR spectra of PAHP3**	**Fig.17 FTIR spectra of PAHP2**	**Fig.18 FTIR spectra of PARP3**
			

Table:2 FTIR analysis

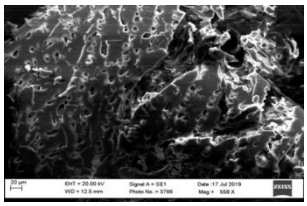
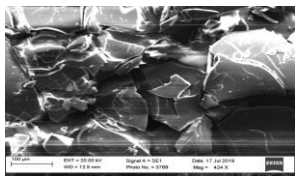
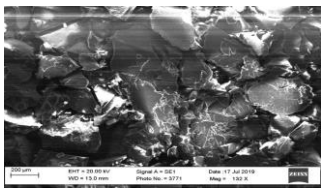
Fig.19 SEM image of AH2	Fig.20 SEM image of AH3	Fig.21 SEM image of AHP2
		

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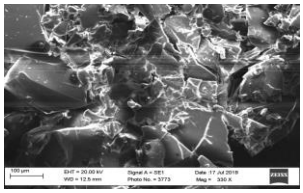
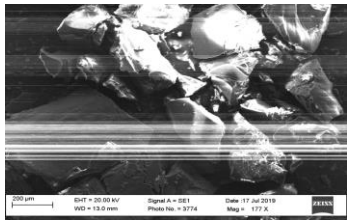
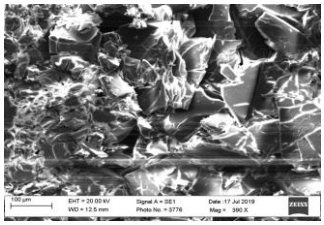
Fig.22 SEM image of AHP3	Fig.23 SEM image of ARP2	Fig.24 SEM image of ARP3
		

Table :3 SEM

Formulations	Percent drug content (%)
AH2	63.104
AH3	49.32
AHP2	49.45
AHP3	27.16
ARP2	53.4
ARP3	32

Table :4 percent drug content

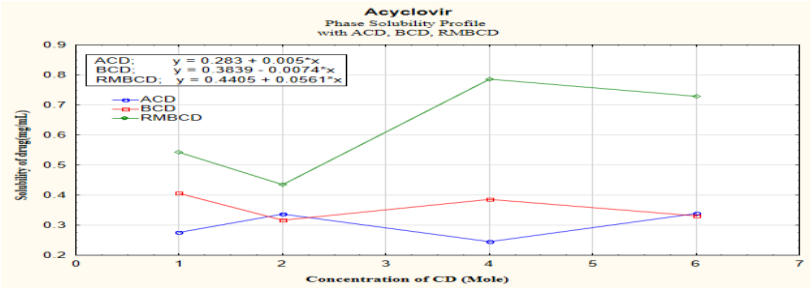


Fig.1 phase solubility graph

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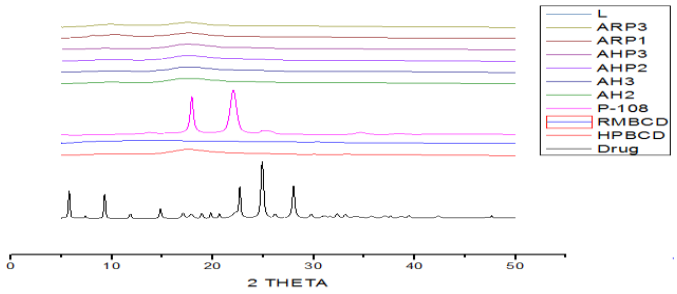

Fig.2 Graph for X-RD

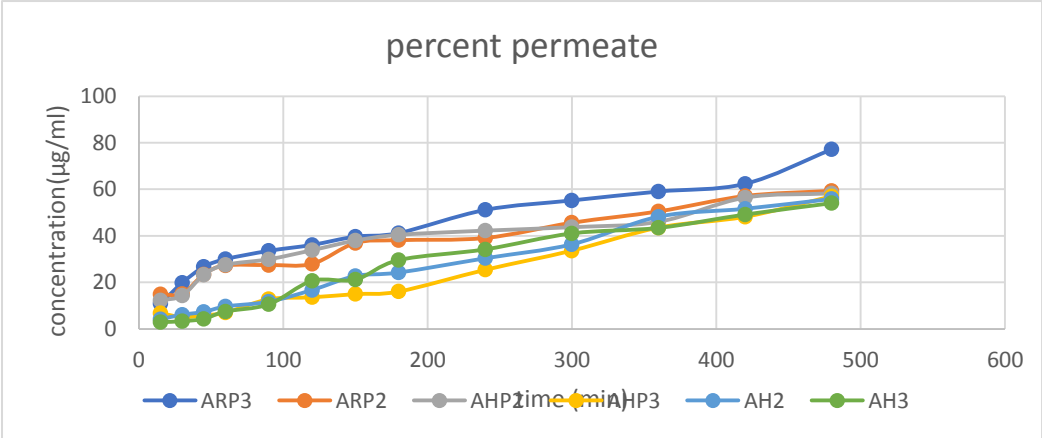

Fig.3graph for percent permeate