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Research article

Design and *In Vitro* evaluation of sustained release matrix tablets of zidovudine hydrochloride: a combination of natural polymers

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ABSTRACT

The current paper was a shot to style a sustained unharness dosage kind victimisation varied grades of hydrophilic polymers, Hypromellose or Hydroxy- propyl alkyl radical polysaccharide (HPMC K15M, HPMC K100M), Sodium alginate and Chitosan additionally incorporated as rate retarding. Material Methods: Laboratory scale batches of six tablet formulations were ready by wet granulation technique (Low shear). Micromeritic properties of the granules were evaluated before compression. Tablets were characterised as crushing strength, friability, weight variation, thickness, Drug content or assay and evaluated for in-vitro unharness pattern for fifteen unit of time victimisation Phosphate buffer of suitable pH 6.8 at 37±0.5°C. Results and discussion: The results obtained discovered that HPMC K15M, Chitosan , Sodium alginate and Ethylcellulose at an acceptable concentration formulation (F4) was able to sustain the drug unharness for fifteen hours and followed Higuchi pattern similar Fickian diffusion. It had been found that every one parameters were at intervals the limit of acceptance. There was slight chemical interaction found between the drug and excipients throughout FT-IR and DSC study thought of in the present investigation. Conclusion: therefore it may be over that combinely polymers at an acceptable concentration will effectively be formulate to sustain the drug unharness.

Keywords: Zidovudine, Chitosan, Sodium alginate, Higuchi, Validation, Drug content.

INTRODUCTION

Oral Oral drug delivery is that the most generally utilised routes for administration that are explored for general delivery of drug via numerous pharmaceutical products of various dose kind. Among them tablets area unit the foremost common oral dose forms offered within the market and most popular by the patients and physicians identical. In long medical care for the treatment of chronic illness conditions, typical formulations area unit needed to be administered in multiple doses, and so have many disadvantages. So as to cut back the downside related to multiple dosing, controlled unleash pill dose kind was developed. A viral infection happens once an epidemic enters the body through such processes as respiratory air contaminated with a virulent disease, consumption contaminated food, or by having sexual contact with an individual World Health Organization is infected with a virulent disease. A infection can also be caused by associate injury. During an infection, the virus invades the within of the body's cells so as to breed. a virulent disease then spreads to different cells and repeats the method.

However, some people are at risk for developing serious complications of viral infection. In addition, certain types of viral infections, such as HIV/AIDS, are not self-limiting and cause serious complications and are eventually fatal. In India, the number of HIV positive cases up to 2006 was 5.7 million. Between 5- 7%adult are infected in at least in 10 urban areas, including Mumbai, Kolhapur, Pune, Hyderabad, Churachandrapura and Kohima. There are numerous dosages forms available as controlled drug delivery system.

Matrix tablets are most promising strategy-based system for controlled drug delivery. They are the most reliable controlled drug

delivery system and could be employed as oral drug delivery system or implantable devices.

Zidovudine belongs to a class (group) of HIV drugs called nucleoside reverse transcriptase inhibitors (NRTIs). NRTIs block an HIV enzyme called reverse transcriptase. (An enzyme is a protein that starts or increases the speed of a chemical reaction.) By blocking reverse transcriptase, NRTIs prevent HIV from multiplying and can reduce the amount of HIV in the body.

Thus, an attempt has been made to formulate the extended-release matrix tablets of Zidovudine HCl and tested for controlled delivery of drug using hydrophilic matrix polymer, Hydroxy-propyl methyl cellulose (HPMC K15M, HPMC K100M) and Chitosan [3].

MATERIALS AND METHODLOGY

Materials

Zidovudine was procured as gift sample from Cipla Ltd Mumbai. Hypromellose or Hydroxy-propyl methyl cellulose (HPMC K15M, HPMC K100M) and Chitosan, Sodium alginate was purchased from Lobachemicals. All chemicals and solvents were used are of high analytical grade.

Method for preparation of tablets Zidovudine, HPMC K15M, 100M, Sodium alginate, anhydrous dicalcium phosphate, were passed through #60 mesh and picked up severally in synthetic resin bag. Wet granulation technique was applied for the batch preparation of matrix tablets. All the materials were sifted to fast combining granulator and mixed for twenty minutes at optimized speed. PVP was dissolved in needed amount of water. The above binder resolution was intercalary to dry combine and mixed for fifteen minutes to induce wet mass. In another beaker chitosan was dissolved in 2% acetic acid soultion and intercalary to the higher than mixture to create a wet mass. Then the resulted wet mass was dried at water temperature of 60°C for forty minutes and capable sieve variety forty. The resulted dried granules were sifted through #20 mesh and processed through Multi mill. The comminuted granules were lubricated with lubricants Finally, the lubricated granules were compressed to formulate pills mistreatment tablet compression machine (Cadmach Machinery Pvt. Ltd, India) with ten-millimeter flat formed punches as given in Table 1.

Micromeritic properties of prepared granules

Prior to compression, granules were evaluated for their characteristic parameters. Angle of repose was determined by funnel method. Bulk density (BD) and tapped density (TD) were determined by cylinder method.

Physical Characterization of Matrix Tablets

The physical properties such as crushing strength, friability, weight variation thickness and assay of compressed matrix tablet for each formulation were determined. Tablet crushing strength was determined for 10 tablets using digital tablet hardness tester and the data reported is the mean of three individual determinations. Friability test was performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break [4, 5].

Preweighed randomly selected twenty tablets were placed in a Roche friability tester and operated for 4 min at 25 rpm. Compressed tablets should not lose more than 1% of their weigh. A weight variation test was performed according to USP30 20 tablets by taking samples from a batch after production of every 100 tablets and randomly from a total batch of 300 tablets using an electronic balance (sartorius, India). The thicknesses of tablets were measured by Vernier callipers. The drug content in terms of assay of each batch was determined in triplicate. For each batch a number of 20 tablets were weighed and crushed to fine powder using mortar and pestle. An accurately weighed of 500 mg of the powder was taken and suitably dissolved in water and analyzed by HPLC after making appropriate dilutions

Table 1: Formulation table of each batch

Ingredients	1	2	3	4	5	6
Zidovudine Hydrochloride	00	00	00	00	00	00
Anhydrous Dicalcium phosphate	50	50	50	50	50	50
HPMCK15M	0	0		0	0	0
HPMCK100M	0	0	0		0	0
Chitosan	0		0	0	0	
Sodium Alginate	0	0	0	0	0	0
Ethyl Cellulose		0	0	0	0	0
PVP	0	0	0	0	0	0
Aerosil						
Talc						
Total Weight	55	55	55	55	55	55

Table 2: Micromeritic properties of prepared granules

Formulation code	Bulk Density (X±SD)	Tapped Density (X±SD)	Angle of Repose (X±SD)
F1	0.763 ±3.18	0.918±1.33	41 ± 2.75
F2	0.775±2.09	0.875±2.68	42 ± 2.12
F3	0.786±1.04	0.896±1.87	42 ± 3.36
F4	0.870±1.25	0.922±2.27	39 ± 1.57
F5	0.798±3.34	0.884±1.89	40± 2.69
F6	0.670±1.24	0.757±2.19	39± 2.29

In-vitro dissolution studies

Release rate of all designed formulations were studied up to 15 hours. The procedure was determined using United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle

method). The dissolution test was performed using 900 ml of Phosphate Buffer of pH 6.8 at 37 ± 0.5°C and 70 rpm. A sample of 15 ml of the solution was withdrawn from the dissolution apparatus at 1 hour interval with the replacement of fresh dissolution medium for 15 hours. The samples were passed through a 0.45 µm membrane filter and diluted to a suitable concentration with phosphate buffer. The absorbance of these solutions was measured at 266 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer.

RESULTS AND DISUSSION

Micromeritic properties of granules

Result shows that all the formulations produced optimal flow properties calculated in terms of compressibility. Table 2 depicts micromeritic properties of the designed formulations. The angle of repose ranged from 39 to 42 which indicates optimal flow ability. In addition to that the tapped density and bulk density for all formulation granules ranged between 0.670±1.24 to 0.870±1.25 and 0.757±2.19 to 0.922±2.27, respectively. *Physical*

Table 3: Physical characterization of the designed formulations

For mul atio n code	verage Weight (mg) X±Sd)	hickness (mmX±Sd)	ardnes s (X±Sd	rug content (%) (X±Sd)	Friab ility (%)
F1	655.6±2.56	89±2.75	.25±1.45	101.32±1.96	0.48%
F2	656.5±1.32	29±2.93	75±2.03	98.44±2.49	0.41%
F3	656.1±4.38	.28±2.19	89±2.78	97.13±3.86	0.5%
F4	655.5±1.29	79±2.32	58±4.15	101.28±3.24	0.31%
F5	655.2±2.53	77±1.76	69±2.36	102.64±2.62	0.4%
F6	658.6±3.38	.68±2.29	58±2.2	100.72±2.23	0.38%

Characterisation of matrix tablets

The physical properties of the designed tablets are given in Table three. These properties were studied by determining crushing strength, friability, weight variation, drug content and thickness of the ready tablets. Crushing strength of the ready tablets ranged from 4.25 to 5.69 kg/cm^2. It had been determined that among all the formulations containing HPMC K15M as an intragranular chemical compound showed highest hardness, this might result to higher binding capability of HPMC K15M than HPMC K100M. The european and United States of America pharmacopeias states that a loss up to a quarter is suitable for breakableness and may be attenuate by increasing the additional granular chemical compound level. within the gift study, the proportion breakableness for all formulations were below one hundred and twenty fifth, indicating that the friability is inside the prescribed limits. All the pill formulations showed acceptable pharmacotechnical properties and complied with the USP specifications for weight variation, drug content, hardness, and breakableness. All the formulations showed uniform thickness. in an exceedingly weight variation take a look at, the pharmacopoeial limit for the proportion deviation for tablets of over 325 mg is ± 10 the troubles. The typical proportion deviation of all pill formulations was found to be inside the on top of limit, and thus all formulations passed the take a look at for uniformity of weight as per official needs. 19-20 Average weight of every formulation tablet ranged from 645 mg to 648 mg. Satisfactory uniformity in drug content were found among completely different batches of the tablets, and therefore the proportion of drug content was over 90%.

In-vitro dissolution studies

Different grades of HPMC like HPMC K15M, HPMC K100M to formulate various Zidovudine matrix tablets and those formulations were subjected to *in-vitro* drug dissolution studies. The dissolution studies were performed in Phosphate Buffer of pH 6.8 for a period of 15 hrs. A Result showed that approximately 35 % of the drug was released within 1 hr for all formulation and 82% of the drug was found to release at the end of 15 hrs. The results also revealed no significant pattern in ethyl cellulose formulation. It was observed that the formulation F6 released fastest and F1 least. It could be reason that in Formulation F1; the combination of HPMC polymers and Chitosan delayed drug release. It was also observed that the formulations containing chitosan prolonged drug release.

The data obtained from *in-vitro* dissolution studies were fitted to zero-order, first-order, and Higuchi release kinetics. The best fit with higher correlation coefficient (r^2>0.98) was found with Higuchi's equation for F4. To confirm the exact mechanism of drug release, the data were fitted by the Korsemeyer-Peppas equation.

$$M_t/M_T = k\, t^n \qquad (5)$$

Where M_t corresponds to the amount of drug release in time t, M_T is the total amount of drug released after an infinite time and k stands for constant related to the structural and geometric properties of the drug delivery system. The value of '*n*' indicates the release mechanism. Regression analysis was performed and values of regression coefficient (R^2) were ranged from 0.993 to 0.9997 for different formulations and slope of 0.43<n<0.51. Hence it can be inferred that the release was based on diffusion. On the basis of the above results, F4 was selected as a promising formulation for further studies.

Drug polymer interaction study

FT-IR Study

pure zidovudine, mixed with the polymer hpmc k15m, anhydrous dicalcium phosphate, sodium alginate and chitosan separately with ir grade kbr and pellets were prepared by applying a pressure of 15 tons in a hydraulic press. the pellets were scanned over a wavelength range of 450 to 4,500 cm^{-1} using an ftir 8400s, schimazu. there was no chemical interaction between zidovudine hydrochloride and the polymers used which is obtained by employing i.r. spectral studies [6].

Figure 1: Percentage Cumulative Drug release from formulations

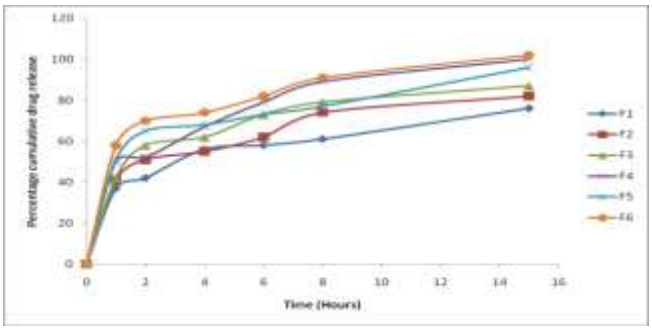


Figure 2: FTIR spectra of selected formulation

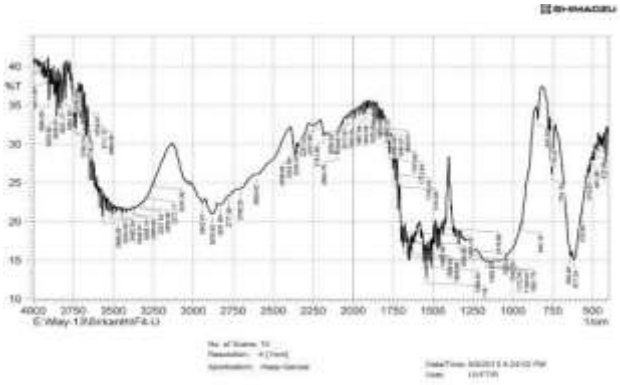
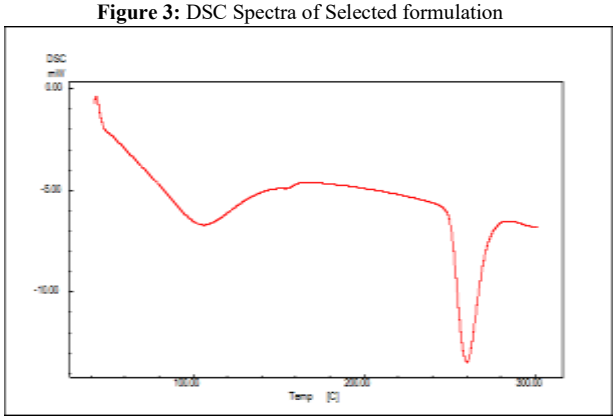


Figure 3: DSC Spectra of Selected formulation



DSC Study

Differential scanning calorimetry (DSC) has shown to be an important tool to quickly obtain information about possible interactions between the active and the excipients, according to the appearance, shift or disappearance of endothermic or exothermic peaks. DSC study was performed using DSC 8000 Perkin Elmer instruments to determine the drug excepient compatibility study. During study a sharp endothermic peak for Zidovudine was obtained at 270^0C corresponding to melting point. But in the formulation there was a slight change in peak temperature and peak shape, with an additional broad peak, which might be due to reduction of the purity level of component and interaction with excipients.

CONCLUSION

The present investigation shows that various grades of HPMC, Chitosan, Sodium alginate and ethyl cellulose at suitable concentration combinely and effectively be used to modify the release rates in hydrophilic matrix tablets prepared by wet granulation technique. Furthermore the *in-vivo* and pharmacokinetic study have to carry out.

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