RESEARCH ARTICLE

Preparation and *In-vitro* Evaluation of Floating Bilayer Tablets of Nefopam HCL as an Oral Modified Release Dosage Forms

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ABSTRACT

Nefopam hydrochloride is a non-opioid analgesic used for acute and chronic pain. Formulation of this drug as a floating tablet could be a good choice because of no need for advanced preparation methods and also gives an accepted extended-release in the gastric media to get rid from multiple daily doses. Adding a bilayer technique means the immediate part with quick dissolution impacts a first analgesic effect with a sustained release from the floating part. In this study, all three preparation methods used direct compression, dry granulation, and wet granulation with different polymers and effervescent materials in different concentrations from all these trials. Only 14 formulas met the criteria of accepted floating part from them only one was taken to be immerged with an immediate release layer to get the best bilayer floating design.

All the formularies pass through ordinary pre and post-compression floating tablet characteristics with different results that permit more comparison between different formulas giving us more knowledge about the nature of drugs, polymers, additives, and method of preparation. The formula called WEN2 contains (HPMC E15 150 mg, Carbapol943 22.5 mg, sodium bicarbonate 45 mg, and tartaric acid 22.5 mg) prepared by wet granulation chosen for best formula design.

Keywords: Bilayer tablet, Floating tablet, Nefopam HCl, Sustained release.

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INTRODUCTION

In the oral dosage form, a high percentage of them are intended to be absorbed by the stomach or intestine. The main challenge is the poor absorpti on due to low retention time in these areas.[1] A delivery system that provides long-time preservation inside this region will offer many advantages like prolonging the time of drug contact with the absorption site and sustained release profile. Gastro retentive drug delivery system is designed depending on the increased retention time of the drug preparation inside the stomach media for a longer time. Many approaches and modifications are applied under this general title.[2] Effervescent floating tablet one of these approaches the idea behind it is the design a formula with a density lower than the gastric media to ensure from residency and withstand against gastrointestinal motility, during this time continues the release of drug and sustained release achieved. The effervescent part in this system plays an important role by producing CO_2 gas when contact with gastric media entrapped inside the formula providing shorter floating lag time and longer total floating period.[3,4] Many factors affected the action of this system like type and frequency of food intake,[5] posture of the patient,[6] emotional state,[7] genders, age,[8] effects of other medications, and diseased state.[9]

Bilayer tablet technology provided many causes, like if the two chemically incompatible drugs were intended to be given together. The separated bilayer tablet will be accepted.[10] Sustained and immediate release immerged together in one dosage tablet.[11] The bilayer tablet also decreased unites intake by the patient that improved their compliance of them.[12]

Nefopam HCL is a non-opioid analgesic used for acute and chronic pain. It is the drug of choice for treatment of postoperative shivering, severe hiccups, and neuropathic pain[13,14] with the dose of (30–90) mg three times daily,[15] short half-life about 4 hours, highly soluble, highly absorbable form gastrointestinal tract (GIT), weak base with pKa 9.2, partition coefficient 3.05 also it is extremely metabolized by liver with low bioavailability about 36%.[16]

This study aims to design a multi-release mode tablet, immediate layer, and sustained layer by effervescent floating system by using different release retardant polymers to optimized best formula according to characteristics of floating bilayer tablet.

MATERIALS

Nefopam hydrochloride (Baoji guokang biotechnology co limited), hydroxyl propyl methyl cellulose E15, carbapol 934

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from, hydroxyl ethyl cellulose (Alpha chemika), sodium aliginate (vegetal) (Rubilabor chemical limited), sodium bicarbonate, tartaric acid (Himedia), Poly vinyl pyrrolidine (Direvo industrial biotechnology), talc (Afco, India), magnesium stearate (Afco, India), lactose (Riedel-deltaen, Germany)

METHODS

Preparation of Immediate Release Layer

Direct compression is the preparation method for this layer. Table 1 summarizes the immediate release composition. All constituents are mixed, then milled by mortar and pestle for 5 minutes. After that, a known weight of the mixture blend with the lubricant (magnesium stearate) gently to be ready for the compression using a punch and die 10 mm.

Evaluation of Immediate Release

Disintegration Test

The thin immediate layer put in disintegration apparatus filled with 0.1 N HCl at 37˚C then recorded the disintegration time.[17]

Dissolution Test

The *in-vitro* release study done by USP dissolution apparatus (paddle) type in 500 mL 0.1 N HCl solution at 37°C, Samples of 5 mL were reserved at a fixed time breaks filtered and slow at the UV of maximum absorbance of 266 nm.[17]

Preparation of Effervescent Gastro-retentive Floating Layer

Three methods of tablet preparation used with drug and additives mounts according to Table 2.

Table 1: Nefopam HCL immediate release layer

Nefopam HCl	*Mannitol*	*Magnesium stearate (Lubricant)*	*Final weight*
30 mg	19.5 mg	0.5 mg	50 mg

Direct Compression

The constituents of the formula are mixed and milled by mortar and pestle for 5 minutes the add a magnesium stearate as a lubricant before compression by tablet machine with 10 mm punch and die.

Dry Granulation

The constituents of the formula were mixed and milled by mortar and pestle for 5 minutes then compressed by tablet machine with low compression force the product screen by a mesh size no 16, this operation repeated until uniform granules were obtained then mixed with magnesium stearate as a lubricant before compression by tablet machine with 10 mm punch and die.

Wet Granulation

The constituents of the formula are mixed and milled by mortar and pestle for 5 minutes, then add a (polyvinylpyrrolidine 10% in ethanol) drop by drop to the mixture until a slurry paste is performed then screen it by a mesh size no. 16, the resultant granules put in the oven to ensure dryness, another screening is done to the dry granules by the same mesh, then mixed with magnesium stearate as a lubricant before compression by tablet machine with 10 mm punch and die.

Evaluation of the Gastro-retentive Floating Part

Friability Test

Using the Roche friabilator 20 tablets were weighed and put in the apparatus with 25 rpm (recycle per minute) for 4 minutes; after that, reweighed the tablets and measured the percent loss.[18]

Hardness Test

Six tablets from each formula were evaluated by Monsanto hardness tester and took the average.[18]

Table 2: Composition of floating formulas

Formula code	*HPMC E15*	*Carbapol 934*	*HEC*	*Sod. alginate*	*Sod. bicarbonate*	*Tartaric acid*	*PVP*	*Lactose*	*talc*	*Mg. stearate*	*Method of prep*
DIN1		80		85	50	25		16.8		3.2	
DIN2	140	25			50	25		16.8		3.2	
DIN3	150	22.5			45	22.5		16.8		3.2	Direct compression
DIN4		80	85		50	25		16.8		3.2	
DIN5	100	30	35		50	25		16.8		3.2	
DIN6	140	25			75			16.8		3.2	
DR1	140	25			50	25		16.8		3.2	Dry granulation
WEN1	150	22.5			45	22.5	11	5.8	3.2		
WEN2	150	22.5			45	22.5	11	5.8		3.2	
WEN3	140	25			50	25	11	5.8		3.2	
WEN4	90	45	30		50	25	8	8.8		3.2	Wet granulation
WEN5	100	30	35		50	25	8	8.8		3.2	
WEN6	100	45	20		50	25	8	8.8		3.2	
WEN7	140	25			75		5.8	11		3.2	

*All ingredients' weights in mg, the amount of Nefopam HCL is 60 mg in each formula and final weight is 320 mg for all.

Content Uniformity Test

Random 10 tablets were taken and milled together, then put in 0.1 N HCl in a water path shaker for 24 hours then measured the amount of the Nefopam HCl by UV spectrometer with a wavelength of 266 nm.[17]

Determination of Floating Lag Time and Floating Duration

The floating duration time and floating lag time (time needed to float the tablet after being immersed in a media) were measured by putting tablets in a 100 mL beaker of 0.1 N HCL then record results.[19]

Dissolution Test

Prepare 500 mL (0.1 N HCL) and use for dissolution test with paddle apparatus type, under 37˚C condition. Set of samples (5 mL) taken in the sequence of (15, 30, 45, 60, 120, 180, 240, 300, 360, 480, 720, 960, 1200, 1440) minutes every sample drawn replaced by fresh media (0.1 N HCL) to keep sink condition then series of samples measured by UV-visible spectrophotometer with 266 nm wavelength.[20]

Variables Affecting Release Profile from Nefopam HCL Floating Matrix Tablets

Effect of Preparation Method

This could be noted in the DIN2, DR1, and WEN3 were prepared by direct compression, dry granulation, and wet granulation, respectively, while it is composed of the same components.

Effect of the Polymer Ratio

In the formulas WEN4, WEN5, and WEN6, different polymer ratios of HPMC: Carbapol934: HEC with the same other conditions.

Effect of type of Lubricant Used

In the formulas WEN1 and WEN2, only the difference is talc as a lubricant instead of magnesium stearate.

Effect of Effervescent part Ratio

The DIN2 formula which contained an effervescent ratio 75:320 while DIN3 formula contained 67.5:320 in this case, the preparation method is direct compression. While in WEN2 and WEN3 the wet granulation is the method of preparation.

Bilayer Tablet Preparation

The best formula of floating part was selected. A known amount of the granules of the selected formula poured in the tablet machine with a punch and die 10 mm then slightly compressed so that a rough side performed then add the granules of immediate release part and compressed the whole tablet.[21]

Evaluation of the Bilayer Tablet

We study the friability, hardness, floating lag time, and floating duration content uniformity and dissolution study as per the ways previously revealed in the floating sustained release layer evaluation.

RESULT AND DISCUSSION

Evaluation of Immediate Release Part

The disintegration time was 1 minute, and complete dissolution occurred within 30 minutes.

Evaluation of Floating Sustained Release Part

The post-compression properties displayed in Table 3 all results occur within accepted levels according to the USP limits. The prepared bilayer tablets illustrated an accepted floating properties and post- compression characteristics of the tablets as shown in Table 4.

Variables Affecting Release Profile from Nefopam HCL FloatingMatrix Tablets

Effect of Preparation Method

Three formulas (DIN2, DRN1, and WEN3) were designed with the same component but in different preparation methods to study the impact of these approaches on the release profile in the dissolution media.

Table 3: Evaluation of floating part

Formula code	*Hardness*	*Friability*	*Content uniformity*	*Floating lag time (minute)*	*Floating duration (hours)*
DIN1	5.5	0.2	94.5	21	15
DIN2	5	0.3	94	30	>24
DIN3	4.5	0.29	93	48	>24
DIN4	4.5	0.21	102	29	13
DIN5	4.5	0.27	95	51	>24 (destructed after 15 hours)
DIN6	4.5	0.18	93	20	>24
DRN1	4.5	0.2	94.5	70	6
WEN1	4.9	0.19	97	13	>24
WEN2	4.8	0.15	98	24	>24
WEN3	5.5	0.17	96	30	>24
WEN4	4.7	0.22	99.2	12	>24
WEN5	4.8	0.25	98	12	>24
WEN6	4.1	0.23	98	10	>24
WEN7	4.4	0.24	97	12	>24

Variables Affecting Release Profile from Nefopam HCL Floating Matrix Tablets

WEN3, DRN1 and DIN2 provide the following release percent in three levels T25% (69, 48, 42), T50% (98, 76, 75), T80% (100, 87, 86). All these formulas appear a good retarding for drug release from their matrixes; this could be attributed to the HPMC E15 polymer effect, which is hydrophilic background systems. Efficient viscous gels regulate water and drug discharge transmission to attain well-ordered release with this water-soluble polymer.

The polymer rapidly hydrates on the external tablet membrane to provide a gelatinous film. Quickly creating a viscous film is important to avoid wetting the internal portion and dissolution of the tablet core. When the original shielding gel coat is created, it manages the diffusion of other media inside the system. As the external gel coat thoroughly hydrates and liquefies, another internal sheet must substitute it and be cohesive and constant enough to prevent media entry and manage drug transmission. Due to this mechanism, the unexpected access of solutions inside the matrix system is organized, and channelizing of dissolution media was efficient by the existence of hydroxypropyl methylcellulose (HPMC) E15 polymer and kept the tablet integrity till the complete drug is released from the matrix.[22] The release profile from the tested formulas met with this explanation but the retardation effect is higher with the direct compression formula (DIN2) which is reach to 95% after 24 hours of the experiment while the others reach to about 100% before 8 hours for WEN3 and 4 hours for DRN1 this clear differences may be attributed to the formulation method where the tablet prepared from fine powder materials that is compressed to create a dense tablet, this impact structure delays the hydration rate and whole the process of exchanging the hydrated layers as mentioned above that will decrease the rate of drug release in the end stages while the WEN3 and DRN1 prepared by wet granulation and dry granulation respectively in these systems the granules formed the consistency of the system provide lower density structure than in direct compression due to less cohesive forces between granules in comparison with the fine powder particles that will permit faster hydration rate and so on earlier discharge of the drug from the matrix, another factors like high water affinity of dry granules and presence of highly soluble PVP in the wet granules might be play a role in drug release especially in the earlier stages.[23]

Effect of Polymer Ratio

The combination of three polymers and partial percent changing do not appear any difference in release profile all of them still releasing over 20 hours. The partial exchange of the HPMC by HEC or Charbapol 934 does not significantly affect the release might be due to their similar action as a hydrophilic polymer that absorbs fluid and forms an outer wetting layer promoting drug dissolution and release outside the system.

Effect of Effervescent Ratio

In this comparison study the percent of the effervescent part is (68:320) in DIN3 and WEN2 and (75:320) in DIN2 and WEN3, clearly the formulas with higher percent appear faster release profile this might be related to the production of larger amount of CO_2 that is made more penetration holes in the matrix promoting more fluid penetration inside and so on release of the dissolved drug these results also detected by SanthaSheela N. B*et al* who prepared floating matrix clarithromycin[24] in case of direct compression the difference is not apparent while in wet granulation state the relation is very clear this variation might be belong to the compact structure of the tablets formulated with direct compression that hindering the penetration of dissolution media easily in spite of pores formed by CO_2 bubbles liberated from effervescent part also the factor related to the hardness of DIN2 which is higher than DIN3 might be play a role in the resistance of the formula to the destruction is directly related to the release of drug, as the porosity decrease the release also decrease because as the preparation be stronger the penetration effect of the dissolution media will be more difficult.[25]

Effect of Type of Lubricant

The effect of lubricant type studied here by comparing the effect of talc powder with WEN1 and magnesium stearate with WEN2 as in the Figure 2 the rate of release is higher with talc preparation compared with magnesium stearate formula. These results were also detected by Beom-Jin Lee, who prepared melatonin tablet. The effect of hydrophobic material on the release rate is well known, like in the case of magnesium stearate, which is coating the granules of the formula preventing the entrance of dissolution media that decreasing the rate of release.[26]

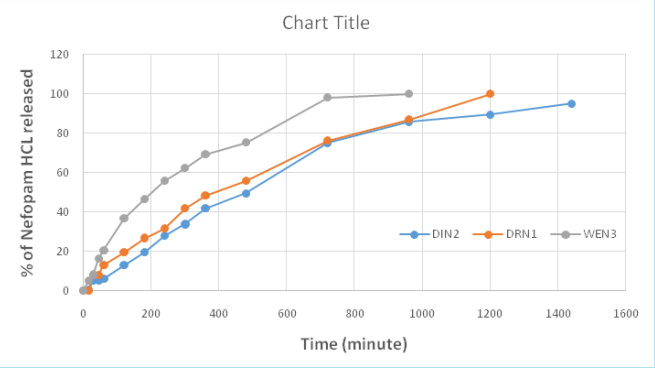

Figure 1: Release of DIN2, DRN1, and WEN3 in 0.1 N HCL

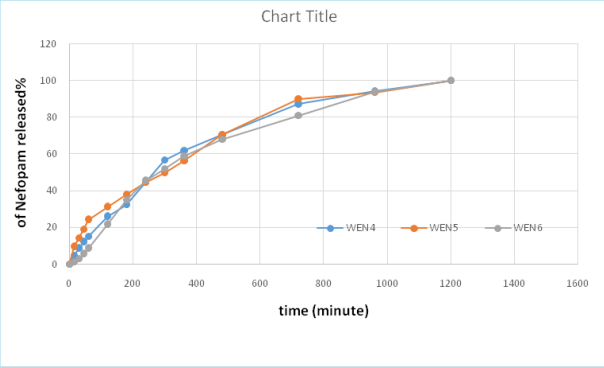

Figure 2: Release of WEN4, WEN5 and WEN6 in 0.1 N HCL

Table 4: Properties of bilayer tablet

Floating lag time (sec)	*Floating duration (hour)*	*Hardness (kg)*	*Friability*	*Thickness*	*Drug content*
30	>24	5	0.6%	4.2 mm	99%

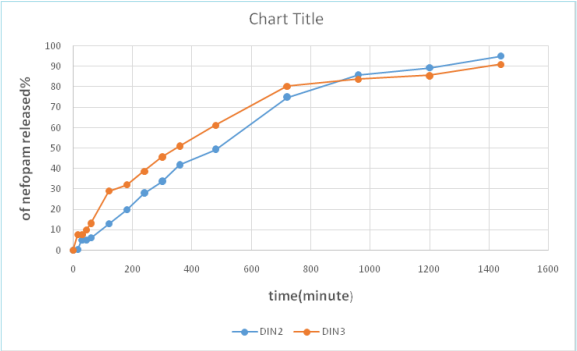

Figure 3: Release of DIN2 and DIN3 in 0.1 N HCL

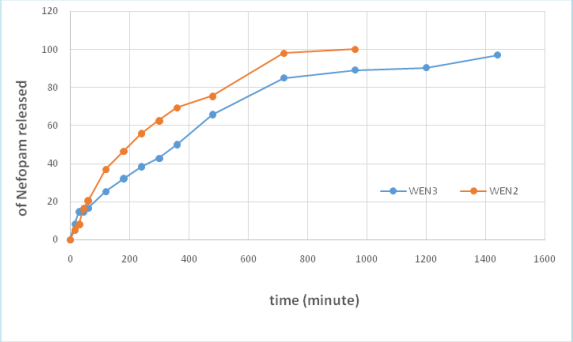

Figure 4: Release of WEN3 and WEN2 in 0.1 N HCL

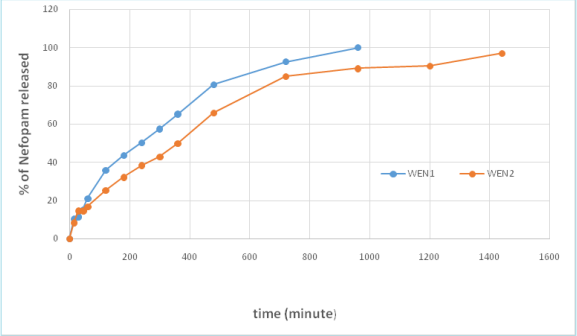

Figure 5: Release of WEN1 and WEN2 in 0.1 N HCL

Bilayer Tablet Evaluation

The prepared bilayer formula displays accepted results according to USP and references.

CONCLUSION

Nefopam HCL formulation as a bilayer floating by combination with a retardant polymers HPMC prolong release time to more than 20 hours despite high solubility of the drug, immediate-release part recorded dissolution time less than 15 minutes that means this preparation covers both acute and chronic pain conditions.

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